Dear Colleagues,

Happy New Year! I hope that the year 2009 will bless you and your family. It is my great honor and pleasure to host the XX World Congress of the International Society for Heart Research on May 13–16, 2010, in Kyoto, Japan. As the President of the World Congress, I cordially invite you to attend the Congress in the most beautiful city in Japan.

Concept and Main Theme

Recent progress in cardiology has closed the distance between laboratory research and clinical cardiology. At the same time, however, the trend towards specialization has promoted sub-discipline activities and led to a proliferation of cardiology and cardiovascular research societies and conferences. At the World Congress, I would like to stress the importance of discussions between basic scientists and clinicians at the same ‘table’, with an over-arching theme of “Bringing Clinicians and Basic Scientists Together towards Integrated Cardiology”. As a consequence of the development of modern biological research techniques, we have analyzed cardiac function and structure at the genetic and cellular levels. In order to understand cardiac function in the whole body, we need to integrate these individual elements. In addition, to understand the pathophysiology of cardiovascular disease, we benefit from insights into biological disciplines other than cardiology, e.g. immunology, endocrinology and neurology. Thus, as the organizing team, we proposed “Paradigm Shift to Integrated Cardiology – Gene, Function and Life” as the main theme of the Congress, to cover
discussions of a wide variety of research topics relevant to understanding the cardiovascular system in health and disease and the application of this knowledge to clinical cardiology.

The Idea for the Congress
The idea is to offer cardiovascular scientists a four-day World Congress in Kyoto, the ancient capital of Japan, in a unique cultural environment that provides an atmosphere that is quite different from the previous Congress in Bologna. I believe that the environment is important for the success of the Congress, and that Kyoto offers a unique venue for participants to enjoy an advanced scientific program in exceptional surroundings. The Congress program will incorporate ISHR Section Meetings so that regional and global discussions can be achieved at the same time.

Scientific Program
The Scientific Program will be composed of Symposia, Special and Award Lectures, Free Communications, a Young Investigator Award Competition, Morning Tutorial Lectures, Luncheon Seminars and Evening Satellite Meetings.

We will start with Morning Lectures, which will provide educational information for young scientists to expand their knowledge base and learn novel techniques for cardiovascular investigation. The main body of the scientific program is composed of Symposia, Special and Award Lectures and Free Communications. A total of 40–45 Symposia will be included in the four-day Congress in parallel sessions. The content of these Symposia will span from basic research to translational and clinical research, from gene to function and life, and will cover a broad range of topics, including the genome, intracellular organelles, ion channels, membrane receptors, signal transduction, cardiovascular development, angiogenesis, cellular damage and protection, cardiovascular diseases, atherosclerosis, stem cells and regeneration, regenerative therapy, clinical advances in cardiology and novel therapeutic targets. Approximately 20 out of the 40–45 Symposia will be planned by the ISHR International Scientific Program Committee chaired by Prof. Metin Avkiran, others will be planned by Section Program Committees as Section-sponsored Symposia, and the remainder will be planned by the local Scientific Program Committee chaired by Prof. Ryozo Nagai as sponsored symposia.

The Special Lectures will include presentations by Prof. Oliver Smithies (University of North Carolina at Chapel Hill), who was awarded the 2007 Nobel Prize in Physiology or Medicine for his work on embryonic stem cells that led to the development of murine gene targeting technology, and Prof. Shinya Yamanaka (Kyoto University), who will speak on his pioneering work on induced pluripotent stem cells. In addition, a number of ISHR Award Lectures will be delivered: (1) the Research Achievement Award lecture; (2) the Outstanding Investigator Award lecture; (3) the Peter Harris Distinguished Scientist Award lecture; and (4) three Distinguished Lectures (Keith Reimer Distinguished Lecture, Janice Pfeffer Distinguished Lecture, and President’s Distinguished Lecture). The Richard J Bing Young Investigator Award Competition will be also be held, and we are anticipating many applications from the very best young scientists in the ISHR community around the world.

A unique feature of the Kyoto Congress will be the incorporation of Section Meetings within the Congress Program. The participating Sections will have the opportunity to hold business meetings and other Section activities, including a session in their own language if they desire. As noted above, several Section-sponsored Symposia will be interspersed within the Congress scientific program.

Free Communications will be in the form of moderated poster presentations. These will be given prominence in terms of space and time and will form an important focal point of the Congress.

Social Program
A get-together on the evening of the first day will provide an opportunity to renew old friendships and make new acquaintances with delegates from all over the world. A short excursion on May 15, to enjoy the Japanese traditional “Aoi Festival”, is a special highlight of the social program. This festival is one of the
most graceful festivals in Japan and has been well preserved since the eighth century, when it began as an occasion to offer prayers for a good harvest following frequent lean years caused by storms and floods. Following the Aoi Festival festivities, we will enjoy an exciting Banquet for all participants at the Conference Hall.

A sightseeing tour of Kyoto city, a short tour of Uji and other social programs are now being prepared. Kyoto is home to nearly 2000 Buddhists temples and shrines, reflecting its long history as the cultural and religious center of Japan. More than 60 museums throughout the city offer visitors the opportunity to view priceless works of art and important cultural objects. Kyoto is also a panorama of the changing seasons, and the timing of the Congress will allow participants to enjoy the lush greenery of early summer.

**Travel Awards**

We are pleased to announce that the ISHR will provide travel awards of US$500 – US$1,000 for more than 110 young investigators from all participating ISHR Sections, with the award recipients to be selected by the relevant Section executives.

**Registration and Abstract Submission**

Meeting and hotel reservations will be available online, and we plan to make the relevant website active beginning in May 2009. Please visit the Congress home page (www.ishr2010.com) regularly for updated information. There are plenty of hotels in Kyoto with very reasonable prices, offering a wide variety of choices.

**Venue of the Congress**

Kyoto International Conference Center (ICC Kyoto) is one of Japan’s leading convention centers and offers all the modern amenities. ICC Kyoto is located in a very scenic area of Kyoto, within verdant and quiet surrounding. Its Japanese-style landscaped garden offers a peaceful setting for Congress participants to meet and communicate informally with each other. Importantly, ICC Kyoto has its own terminal on the subway from Kyoto station, thus offering very convenient access from downtown Kyoto City. Kyoto Station itself has good access from Kansai International Airport (60 min by train) and from Tokyo (2 hours and 15 min by Shinkansen train).

Because all of the major ISHR Sections will hold their Section meetings in conjunction with the ISHR World Congress, we are expecting a total of 2000 participants from all over the world. You are cordially invited to share in the excitement and success of the World Congress 2010 in Kyoto.

Masatsugu Hori, M.D., Ph.D.

President, the ISHR XX World Congress; President, Osaka Medical Center for Cancer and Cardiovascular Diseases; Professor Emeritus of Osaka University Graduate School of Medicine

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Evolution is often compared to a tree with many branches; some branches grow vigorously, while others whither and die. Their fate is ordained by natural selection as some of the weak branches are unable to withstand the destructive powers of the environment. Survival of the fittest is a challenge to the growth of the tree of life.

Like biological growth, new medical therapies are also subject to natural selection. New ideas only survive if they are useful. In the treatment of disease, new therapies persist if they benefit the patient. I write here of the natural selection of an idea: visualization of the coronary arteries in man. Many attempts at visualization fell by the wayside, while others brought us closer to the goal.

Many different approaches were tried to visualize the coronary arteries in man, including needle puncture of the ascending aorta or the carotid artery, a transaxillary approach, and arresting systemic blood flow by inflating a balloon in the ascending aorta. The variety of the names given to these methods illustrates the variety of the approaches: thoracic aortography, retrograde aortography, coronary arteriography, percutaneous selective coronary cinearteriography, guided angiography, and percutaneous transaxillary selective coronary arteriography. Early x-ray techniques were also primitive. I still remember the loud clatter caused by the changing of cassettes during angiography in the early 1940s. It is not surprising that today the memory of some of these methods evokes a shudder. How could we do this to our patients? As late as 1959, an article was published in which the authors visualized the coronary arteries by intrathoracic needle puncture of the ascending aorta with a suprasternal approach, advancing the needle tip to a position slightly above the aortic sinus followed by rapid injection of a radio-opaque medium. The authors added, “To improve our coronary arteriography in more recent studies, we have induced cardiac arrest pharmacologically.” In 1948, Hoyos and Gomez del Campo used an equally daring technique, “…the long needle is introduced into the left interspace, 2 cm outside the left border of the sternum. It is directed backward and a little inward for a distance of about 10 cm into the thorax. Rhythmic pulsation of the needle or fluoroscopic observation will show when the aorta has been entered.”

Much later, Schelbert wrote, “While the lineage of each of today’s commonplace techniques can indeed be traced back to the innovations of our predecessors, we are frequently less cognizant of the blind alleys through which we tried and abandoned. Before openly accepting the glowing promise of today’s innovations, I am always reminded of a talk entitled, “The Way We Were” given by Kurt Amplatz at a June 1989 meeting. During that talk, he showed a film from the 1950s about the then promising technique of left heart catheterization via direct cardiac puncture. The statement that more than one hundred cases had been performed, with a mortality of only one percent, made many shift uncomfortably in their seats to think about which of our current techniques would endure, and which would join direct cardiac puncture.”

The physicians who used these dangerous approaches were honestly convinced of the validity of their methods. The territory which they were exploring was uncharted, and their work has helped to prepare us for more viable approaches. But progress is slowed when authors cling to their prejudices, defending their ideas by resorting to their authority. The only authority in science is Truth.

These developments in the field of coronary visualization have helped to stimulate the development of catheter-based interventions. Here, too, only the fittest ideas survived. Early catheters came in all shapes and sizes, including single and double lumen and loop-ended, with the loop placed directly above the aortic valve. Finally, after natural selection had done away with direct puncture, the use of injection of the contrast medium through a catheter became the method of choice. Here, the method developed by Seldinger was most helpful, but it remained the strong belief of all who attempted coronary angiography that direct catheterization of the coronary artery was courting disaster. The advice of the Nobel laureate Andre Cournand carried much weight when he warned that such a procedure would certainly lead to deadly myocardial ischemia. This is an example how advice based on authority can stifle progress.

In October 1958, Mason Sones was working at the Cleveland Clinic. As the contrast material was injected through the catheter, with the tip located just above the aortic valve, Sones relates that, “I hit the switch to initiate a cine run. When the injection began, I was horrified to see the right coronary artery become heavily opacified and realized that the catheter tip was actually inside the orifice of the dominant right coronary artery. I shouted, ‘Pull it out.’” Sones was prepared to perform open cardiac massage, but the patient was not fibrillating. He was in asystole. When Sones ordered the patient to cough, normal sinus rhythm ensued. Sones related, “Using the ensuing days, I began to think that the accident may point the way to the development of a technique which we had been seeking.”

Mason Sones was born in Mississippi in 1918. He attended medical school at the University of Maryland and had his residency at the Henry Ford Hospital in Detroit. He then transferred to the Cleveland Clinic, where he did his major work. He died in 1985 of bronchogenic cancer. Sones was an unforgettable person: his passionate honesty made him appear rude in the defense of what he believed to be the truth. When he visited

(continued on page 6)
Dear Colleagues,

This has been a difficult column to write because I have not found a unifying theme. We are in the “low season” for the ISHR - that inconvenient trough between one peak of World Congress adrenaline and the next one during which we all seem to hibernate for a while, being too far from both the last and the next Congress. The excitement and clamor elicited by Bologna ’07 have subsided, we have for the most part lost the weight gained in those Italian restaurants, and Kyoto ’10 seems still to be a long way in the future (but not really, if you think about it). At the time of this writing, most of us are emerging from the torpor of the holidays, still trying to remember to write “2009” instead of “2008”at the end of the date. Fortunately, no acute crises are threatening our Society, we do not face bankruptcy, and we are among the few institutions that don’t need a bailout from the government. Yes, the stock market has crashed and the weather in Kentucky has been brutally cold (reaching -20 degrees Celsius), but neither of these issues is likely to intrigue most of you. So, what is the ISHR President supposed to write about?

Not about politics. In the past, this newsletter has been used by one of my predecessors to peddle leftist propaganda. I think that is deplorable. When I became President, I made a decision never to use HN&V to enunciate political opinions, of any kind.

Ah, here is an idea. What about describing what I regard as the salient qualities that are necessary for a career in academic medicine? I have been pondering this issue for a while and one of these days I would like to write about it. But on second thought, I think I should leave this topic for the terminal segment of my Presidency. Another project that has been brewing in the back of my mind is to describe the life and work of William Harvey (the guy who discovered the circulation of the blood). Probably a good idea but I’m still reading about him; so, I need to acquire a better knowledge of the man before I give you a report. Perhaps I could write about history (one of my favorite subjects), but then I’m afraid that this may not be the favorite topic for most of you. As a last resort, I could lament my frustrations with the continually shifting world of technology (whereby as soon as we become moderately familiar with a computer program, a gadget, a device, or whatever, we are forced to experience the stress of learning another one); that would give me plenty to write, but I fear I would appear to be an old relic.

What, then, should I write about? Oh yes, now I remember. One thing I need to do is exhort the organizers of the Kyoto World Congress to be careful in selecting their invited plenary speakers. At the ’07 World Congress in Bologna, I was stunned when I heard an invited speaker state, during a high-profile lecture and with great emphasis, something to the effect that “the 2007 World Congress of the ISHR has nothing to do with human health” (I may be paraphrasing, but this was the essence of the assertion). This was a remarkable statement. Think about it: this individual is selected to deliver a highly honorific lecture at a World Congress in front of an international audience and what does he do in his lecture? He insults the very Society that bestowed this honor upon him. He uses the lecture to inform us that all of the research that was presented and discussed in Bologna had “nothing to do” with human health. I’m sure the people who were in the audience with me were relieved to learn that the scientific work we shared in Bologna - the hard-earned fruit of our daily struggle to understand pathologic processes and find therapies that alleviate, cure, or prevent them - is for naught and does not contribute anything to fighting human disease or promoting human wellness; it’s all a useless academic exercise, a waste of time and money. Very good. Although this vituperative statement is so obviously ridiculous that it does not even warrant a rebuttal, two questions came to my mind: (i) how much ignorance of science does it take for someone to actually believe that basic research has nothing to do with human health? and (ii) how much paucity of common sense does it take to select the setting of an honorific lecture to hurl this slight at your hosts? So, here is my message to the Kyoto World Congress organizers: please be judicious in selecting your invited lecturers!
Speaking of Kyoto, it’s hard to believe that, by the time you read this column, our next World Congress will be only about 1 year away! Kyoto ’10 promises to be another memorable event in our Society’s history. You can look forward to an outstanding meeting that will combine a state-of-the-art scientific menu with a superb social and cultural program, as one has come to expect from a consummate organizer of the caliber of Matt Hori. The Congress will be held in a lovely location and at a charming time of the year. In keeping with the legacy of Bologna ’07, it will encapsulate the 2010 meetings of four ISHR sections: Chinese, European, North American, and Japanese (in addition, the Australasian and Latin American Sections will participate and contribute symposia, speakers, etc.), which will greatly strengthen the impact and positive energy of the conference. A record number of travel awards will be available to young investigators/trainees. I hope you will plan to attend Kyoto ’10; please mark your calendar for May 13-16, 2010.

Alas, I still have not found a theme for this column, so here is another idea. Why don’t I use this opportunity to divulge a proposal that has been in the back of my mind for a while? It pertains to the relatively low penetration of our Society in the cardiovascular scientific community (i.e., the proportion of cardiovascular scientists who are not ISHR members is much greater than that of those who are). In the past I have exhorted every member of the International Council to recruit 10 new ISHR members (if everybody accomplishes such a recruitment, over 200 investigators will join us). By the same token, I would like to exhort each of you to recruit another member. This ought not to be very arduous. If you look around, you will likely find that (unfortunately) many of your colleagues are not ISHR members and, so, it is not difficult to identify one that would understand the benefits associated with membership and would decide to join our Society. This is a simple idea, but if implemented, this grassroots recruitment effort could literally double the size of the ISHR. I hope that you will agree that the ISHR needs to expand, and will help us achieve this goal.

As I am about to make one more attempt at finding a unifying theme, the computer informs me that I have reached my word limit for this column. So, here it is, a potpourri of unrelated, though genuine, thoughts. Isn’t life a bit like this?

References


Richard J. Bing, M.D.
PP2Ce - A Molecular Link between Protein Homeostasis and Cardiac Contractility?

I am very honored to have been selected as the co-winner of the 2008 Young Investigator Award at the XXX Annual Meeting of ISHR North American Section held in Cincinnati, OH, for my work focusing on the functional characterization of a novel ER transmembrane phosphatase, PP2Ce, in ER stress regulation and SR calcium cycling. I obtained a BS degree in Microbiology and a MS degree in Genetics from Fudan University, Shanghai, China. I came to the United States to start my PhD training in Dr Yibin Wang's lab at UCLA where, under the guidance of Dr Wang, I initiated two research projects designed to determine the role of novel type 2C protein phosphatases (PP2C) in the pathogenesis of cardiomyopathy. From these studies, we found that one of these interesting phosphatases, PP2Ce, is not only a potent regulator of IRE1 activity in ER stress regulation, but also an important direct regulator of Phospholamban (PLB) Thr-17 phosphorylation and cardiac contractility. Therefore, PP2Ce might offer an exciting molecular link between protein homeostasis and cardiac contractility.

ER Stress Response in Heart Disease
The endoplasmic reticulum (ER), also called the sarcoplasmic reticulum (SR) in myocytes, is a central organelle that carries out various biological processes including protein synthesis, secretion and post-translational modification and calcium homeostasis. Accumulation of unfolded/misfolded proteins inside the ER triggers an integrated signaling response, collectively termed the ‘unfolded protein response’ (UPR) or ‘ER stress response’, to attenuate de novo protein synthesis, enhance ER folding capacity, and promote degradation of unfolding/misfolded proteins (Ref. 1).

Cardiac myocytes have a unique requirement for both a high level protein flux and a dynamic SR calcium flux to maintain normal contractile function. Elevated UPR gene expression is reported in hearts subjected to pressure-overload, Angiotensin II treatment, ischemia, post-myocardial infarction or hypoxia. While several studies suggest that ER stress induction contributes to myocyte apoptosis and heart failure, other reports indicate that some aspect of UPR is cardioprotective. It is clear that in heart, as in other organs, balancing the protective vs the damaging effects of ER stress signaling is highly critical to normal function and disease progression.

The Missing Component in IRE1 Mediated ER Stress Signaling
The ER stress response is orchestrated by three proximal ER resident transmembrane sensors: inositol-requiring protein-1 (IRE1), activating transcription factor-6 (ATF6) and protein kinase RNA (PKR)-like ER kinase (PERK). All of these sensors are kept in an inactive state by the ER resident chaperone, BIP, via direct interaction under basal conditions. Through direct competition for interaction, mis/unfolded protein in the ER

**Figure 1. PP2Ce is a bona fide IRE1 phosphatase.**

A. Identification of PP2Ce as an IRE1 interacting protein. INS-1 pancreatic β-cell lines, expressing IRE1α-K599A C-terminally tagged with both FLAG and HA tags, were subjected to sequential purification using anti-FLAG and anti-HA affinity columns. The IRE1α interacting proteins were detected by Coomassie blue staining and further identified by LC/MS/MS mass spectrometry. NS, nonspecific.

B. PP2Ce suppresses the IRE1 downstream signaling cascades via direct dephosphorylation. HEK293 cells were transiently transfected with the plasmids as indicated. Forty-eight hours later, the phosphorylation status of IRE1 was determined by the mobility in the SDS-PAGE gel. In a duplicate assay, the IRE1 mediated splicing of Xbp-1 was examined and quantified via RT-PCR analysis. The result from three experiments is presented as mean±SD. * P<0.01.
dissociates BIP from all three stress sensors, thereby triggering the activation of their respective downstream signaling pathways (Ref. 2).

Given its functional significance, it is not surprising that ER stress is a highly regulated process. For instance, upon BIP dissociation, IRE1 homodimerizes through the ER luminal domain and transautophosphorylates its cytosolic domain, resulting in the activation of its RNase domain. Then, activated IRE1 can effectively splice out the noncanonical intron of transcriptional factor XBP1 and hence turn on XBP1 transactivation activity through an open reading frame shift to induce the expression of genes involved in ER protein folding and degradation. On the other hand, IRE1 also promotes ASK1/JNK-mediated apoptotic cell death if the ER stress cannot be resolved. Although the molecular mechanism of IRE1 activation has been extensively explored, the IRE1 deactivation mechanism required during the ER stress recovery phase remains elusive. Recent studies demonstrated that IRE1 is rapidly dephosphorylated upon removal of ER stress, indicating the presence of an IRE1-specific phosphatase in the cell.

Through biochemical purification, we identified a novel ER membrane phosphatase, PP2Ce, which specifically interacts with IRE1 and attenuates its activation via direct dephosphorylation (Fig 1). In addition, we discovered that PP2Ce could effectively suppress the IRE1-mediated XBP1 splicing as well as the ASK1/JNK signaling cascade. Furthermore, we provided evidence that the enhanced association between IRE1 and PP2Ce is likely the underlying mechanism of PP2Ce-mediated IRE1 deactivation upon ER stress. Lastly, we demonstrated that PP2Ce does not participate in the negative regulatory mechanism of the PERK signaling cascade, suggesting that PP2Ce is a specific IRE1 phosphatase in ER stress signaling. In conclusion, the discovery of PP2Ce as a unique IRE1 phosphatase provides a missing piece of the ER stress signaling module.

**Regulation of SR Calcium Cycling and Cardiac Contractility by PP2Ce**

In myocytes, SR is also a critical organelle for calcium release and uptake during systolic contraction and diastolic relaxation. Defects in SR calcium cycling are a major cause of contractile dysfunction and arrhythmia in failing hearts (Ref. 3). PP2Ce mRNA is expressed in many different tissues; however, the highest levels are found in brain, heart and diaphragm based on Northern blot analysis. The high level of PP2Ce expression in the heart suggests that PP2Ce may be involved in regulating other SR protein phosphorylation in addition to its regulation of the ER stress sensor, IRE1. Several critical components of the SR calcium cycling machinery such as PLB, RyR, SERCA have been reported to be regulated by Ser/Thr phosphorylation.

Using a candidate approach, we found that PP2Ce expression in rat neonatal ventricular myocytes significantly blocked CaM kinase-dependent Thr-17 phosphorylation of PLB induced by isoproterenol (ISO). In contrast, PKA-dependent Ser-16 phosphorylation of PLB was not significantly affected at lower doses and only marginally affected at very high doses. This remarkable specificity suggested that PP2Ce can potentially function as a PLB phosphatase specifically directed against CaM kinase phosphorylation.

To further assess the functional impact of PP2Ce on SR calcium regulation, we expressed PP2Ce in adult myocytes and measured intracellular calcium cycling with or without ISO stimulation. There was no significant effect of PP2Ce expression on basal SR peak calcium transients during systole or calcium decay during diastole. However, as shown in Figure 2, PP2Ce expression significantly blunted the ISO-induced increase in the Ca^{2+} transient as well as the acceleration of calcium decay. These data suggest that PP2Ce in heart may also modulate βAR regulation of contractility by attenuating CaM kinase-dependent phosphorylation of PLB.

(continued on page 11)
CAMKII Negatively Regulates Calcineurin-NFAT Signaling in Cardiac Myocytes

It was a great privilege to present my data and a honor to be the co-recipient of the Young Investigator’s Award at the 2008 XXX North America Section Meeting in Cincinnati, Ohio, for my work describing the regulation of NFAT nuclear translocation in cardiac myocytes by Ca\(^{2+}\)-calmodulin dependent protein kinase II (CaMKII) phosphorylation and subsequent inhibition of calcineurin. I became interested in myocardial calcium homeostasis and its role in the pathogenesis of cardiac hypertrophy and failure during my doctoral work and postdoctoral fellowship at Temple University in Philadelphia, Pennsylvania. During my doctoral work, I examined how a physiologic stress, exercise training, impacted cardiac structural and functional remodeling in hypertension. I completed my postdoctoral fellowship at Temple University School of Medicine in the lab of Dr Steven R. Houser where I worked to define molecular mechanisms involved in the pathogenesis of cardiac hypertrophy and dysfunction. I recently joined the Cardiovascular Diseases department at Boehringer-Ingelheim Pharmaceuticals, Inc., where I continue my work to help define new therapeutic treatment options for use in heart disease.

Ca\(^{2+}\) Mediated Cardiac Signaling

Cardiovascular diseases such as hypertension and myocardial infarction raise the contractile stress on the heart. This requires reflex responses (primarily via the sympathetic nervous system) that increase cardiac systolic stress generation by producing increases in myocyte [Ca\(^{2+}\)]. When excess contractile stress is persistent it leads to cardiac hypertrophy and over time is associated with arrhythmias, myocyte death and eventually congestive heart failure. The links between persistent increases in myocyte Ca\(^{2+}\), pathological hypertrophy, cardiac arrhythmias and myocyte contractile abnormalities have been studied but are still not well established.

Increased myocyte Ca\(^{2+}\) activates calcineurin, a phosphatase that dephosphorylates and thereby induces nuclear translocation of NFAT: NFAT, in turn, is involved in the induction of pathological cardiac hypertrophy and prosurvival signaling (Refs 1 and 2). Increased myocyte Ca\(^{2+}\) also activates cytoplasmic CaMKII (CaMKII\(_{\delta}\)), which phosphorylates a number of critical target proteins involved in Ca\(^{2+}\) regulation (Ref. 3). While the effects of CaMKII on individual Ca\(^{2+}\) regulatory proteins is fairly well described, its role in the regulation of NFAT-mediated cardiac gene expression and cell death are not well understood. In addition, recent studies in hypertrophied and failing hearts have shown that CaMKII activity is increased, and this activity is associated with cardiac dysfunction (Ref. 4).

Does CaMKII Regulate NFAT-Calcineurin Signaling?

The present research was designed to determine if activation of CaMKII\(_{\delta}\) is involved in the regulation of NFAT...
nuclear translocation and if so, to define the molecular signaling pathway involved. Our results clearly show that, at least under our experimental conditions in neonatal ventricular myocytes, activation of CaMKII\textsubscript{δc} with a HA-tagged constitutively active CaMKII\textsubscript{δc} adenovirus (CaMKII-CA) increases NFAT phosphorylation state (indirectly) and reduces NFAT nuclear translocation, while inhibition of CaMKII\textsubscript{δc} with dominant negative CaMKII\textsubscript{δc} (CaMKII-DN) reduces NFAT phosphorylation (indirectly) and induces NFAT translocation from the cytoplasm to the nucleus (Fig. 1).

The most novel aspect of the current study is how CaMKII achieves these differences in NFAT phosphorylation through a direct effect on calcineurin. All other kinases that alter calcineurin-NFAT signaling (GSK, p38m, JNK, PKA, MEKK1, CKII) do so by directly phosphorylating the N-terminus of NFATc1-c4 within the regulatory domain that controls nuclear shuttling by masking and unmasking a nuclear localization sequence. However, CaMKII did not directly phosphorylate NFAT in our hands, but instead directly phosphorylated calcineurin. These data were confirmed using a phosphorylation specific antibody against the Ser\textsubscript{197} site on calcineurin, a site previously shown to be phosphorylated by the autophosphorylated form of CaMKII, thereby resulting in partial inactivation of calcineurin (Ref. 5). Phosphorylation of calcineurin at Ser\textsubscript{197} was observed in both neonatal rat ventricular myocytes expressing CaMKII-CA while PLB phosphorylation was increased at Thr\textsubscript{17} consistent with increased CaMKII activity. A reduction in ANP abundance was observed in myocytes expressing CaMKII-CA, consistent with reduced hypertrophic signaling.

Figure 2. (A) To demonstrate protein abundance and phosphorylation state of proteins involved in this signaling cascade, protein extracts were made from cultured neonatal myocytes expressing CaMKII-CA or CaMKII-DN, while GFP-transfected cells acted as a control. The phosphorylation of calcineurin (Cn) at Ser\textsuperscript{197} was detectable only in neonatal rat ventricular myocytes expressing CaMKII-CA while PLB phosphorylation was increased at Thr\textsuperscript{17} consistent with increased CaMKII activity. A reduction in ANP abundance was observed in myocytes expressing CaMKII-CA, consistent with reduced hypertrophic signaling.

(B) An increase in phosphorylation of calcineurin at Ser\textsuperscript{197} was observed in hypertrophied feline left ventricular tissue.

Figure 3. A representative schematic of the proposed CaMKII-calcineurin interaction. The phosphorylation of calcineurin by CaMKII results in reduced calcineurin activity leading to reduced basal and calcium mediated NFAT translocation.
that increases in myocyte Ca\textsuperscript{2+} activates two parallel signaling cascades with opposite effects on calcineurin activity, and thereby on NFAT nuclear translocation and hypertrophic signaling (Fig. 3).

Conclusion
Our findings demonstrate a previously unappreciated role of cytoplasmic CaMKII in cardiac myocytes. Collectively our results demonstrate that the constitutively activated form of CaMKII directly phosphorylates calcineurin and inhibits its activity, resulting in reduced NFAT nuclear translocation, and increased myocyte apoptosis (data not shown). In cardiac disease states in which CaMKII activation is known to be increased, we hypothesize that “hyperactivation” (constitutive) of CaMKII disrupts NFAT signaling and contributes to cardiac structural and functional defects. Thus,

as suggested by others (Ref. 6), CaMKII inhibition may be an effective strategy for improving myocardial function in heart disease.

Scott M. MacDonnell (Ridgefield, CT) was one of the two winners of the Young Investigator Award competition during the XXX Annual Meeting of the North American Section (Cincinnati, OH; June 2008).

PP2Ce - A Molecular Link Between Protein Homeostasis and Cardiac Contractility? (continued from page 8)

Conclusions and Future Directions
Although ER stress signaling and SR calcium cycling are confined in the same intracellular compartment, little is known about their potential interaction under physiological or pathological conditions. The specific activity of PP2Ce towards not only the ER stress sensor, IRE1, but also the calcium cycling regulator, PLB, strongly suggests that ER protein translation, folding and degradation is tightly coordinated with the maintenance of ER calcium homeostasis, especially in beating cardiac myocytes. Future studies will be needed to fully understand the functional importance of this mechanistic interaction mediated by PP2Ce in heart.

I wish to acknowledge Ms. Asuka Ota, Drs Peipei Ping, Thomas Vondriska, Sarah Warburton, David Ron, Hongmei Ruan and Shuxun Ren for their significant contribution to this study.

References

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ISHR AWARDS
Nominations for the 2010 Outstanding Investigator Award, the Research Achievement Award, and the Peter Harris Distinguished Scientist Award are now being accepted (deadline: November 30, 2009).

The deadline for receipt of applications for the 2010 Richard J. Bing Young Investigator Award is January 10, 2010.

Details of the nomination and application procedures can be found at www.ishrworld.org under the "ISHR Awards" tab.

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References
**CONTRIBUTION OF STRUCTURAL HETEROGENEITY TO STRETCH-INDUCED ARRHYTHMIAS EXAMINED IN VENTRICULAR TISSUES AND ISOLATED MYOCYTES**

It was a great honor for me to receive the 2008 Young Investigator Award at the 25th Annual Meeting of the Japanese Section in Yokohama, Japan, for my work entitled ‘Contribution of structural heterogeneity to stretch-induced arrhythmias examined in ventricular tissues and isolated myocytes’. I am currently a Ph.D. candidate working with Profs. Sugiura and Hisada in the Graduate School of Frontier Science at the University of Tokyo. This work was carried out in close cooperation with Dr Inagaki in the National Cardiovascular Center Research Institute and Dr Nishimura in the Department of Cardiovascular Medicine at the University of Tokyo. In this work, we used novel stretching devices and optical recording techniques to study the mechanisms of stretch-induced arrhythmias at both the cellular and tissue levels. In order to explain the experimental findings, we also performed a computer simulation study.

**Mechano-electric Feedback and Stretch-induced Arrhythmias**

It is well known that alterations in the mechanical state of the myocardium affect its electrophysiological properties. This phenomenon, termed mechano-electric feedback, is considered to play a significant role in the genesis of cardiac rhythm disturbances. In particular, this effect is exaggerated in various diseased states in which alterations in the refractory period and conduction velocity constitute the substrate for arrhythmogenicity. Stretch-activated channels (SACs) have been regarded as the most likely candidates for primary transducers of mechanical stress, but there is a huge gap between laboratory findings and studies of clinical arrhythmias at the organ level. Accordingly, the purpose of this study was to examine how the cellular response to stretch leads to arrhythmias in the heart in experiments carried out at the cellular and tissue levels.

**Cellular Study**

In experiments at the cellular level, we developed a novel carbon fiber technique to stretch single isolated cardiomyocytes (Ref. 1). We measured membrane potential by using a voltage-sensitive fluorescent dye (di-8-ANNEPS) with an optical recording system (Ref. 2).

Our data demonstrated that the membrane potential responds to stretch in a length-dependent manner, and that when the amplitude of stretch exceeded 15%, action potentials were triggered in some myocytes. These effects were inhibited by the addition of GsMTx-4, a known blocker of SACs (Fig. 1A, right figure).

**Tissue Study**

The next step was to determine how such cellular responses lead to arrhythmias. We performed a tissue level study to examine whether arrhythmias are also initiated in an amplitude-dependent manner in the heart.

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**Figure 1. A. Cellular study. (Left figure)** Carbon fiber technique for applying stretch to a single isolated myocyte. **(Right figure)** Membrane potential changes in response to axial stretch. The membrane potential depolarized in a stretch-dependent manner (Control), but the response was inhibited by an inhibitor of stretch-activated channels (GsMTx-4).

**B. Tissue study. (Left figure)** Arterially perfused free ventricular wall was attached to the stretching device. Bead markers are seen. **(Middle figure)** Time-lapse images showing the propagation of the focal excitation initiated by a medium (10%) stretch. **(Right figure)** Inhomogeneous thickness distribution. In most cases, focal excitation was initiated from the thinner area.
For this experiment, we developed a means by which uniaxial global stretch could be applied to arterially-perfused rabbit right ventricular free wall using a linear motor. We simultaneously recorded the electrical and mechanical changes. Membrane potentials were measured using an optical mapping system and the stretch was monitored by tracking the beads as landmarks (Ref. 3).

Although uniform stretch was applied to the ventricular tissue, the membrane potentials depolarized heterogeneously and the action potential was evoked in a focal spot (Fig. 1B, middle figure). Such spatial heterogeneity became prominent when global stretch of intermediate amplitude (10%) was applied. Morphometry of the tissue revealed that such focal spots were located where the tissue was thinnest (Fig. 1B, right figure).

**Figure 2. Simulation study.**

*Left figure* Finite element method (FEM) model of the ventricular wall tissue (seen from the endocardium).

*Right figure* Serial images showing the changes in membrane potential of the ventricular tissue in response to intermediate (10%) stretch (seen from the epicardium). It is clearly seen that the focal excitation from the thinner area evolved into a sustained spiral wave.

Simulation Study

Our experimental study showed that heterogeneous excitation was achieved in response to global stretch of medium intensity. Therefore, we hypothesized that global stretch of medium intensity, rather than an intense stretch, triggers fatal reentrant arrhythmias and we subsequently examined this hypothesis in a computer simulation.

In the simulation, we developed a 3-D model of excitable and contracting cardiac tissue (Ref. 4). The model was based on the finite element method with real tissue morphology, and a mathematical model of stretch is modulated by the inhomogeneous structure of the ventricular wall to cause heterogeneous excitation. This effect becomes manifest in response to stretch of medium intensity and may trigger fatal arrhythmias.

**References**


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**Kinya Seo** (Tokyo, Japan) was the winner of the Young Investigator Award competition during the XXV Annual Meeting of the Japanese Section (Yokohama, Japan; December 2008).


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**In Memoriam**

**Dr Phillip Poole-Wilson**

1943 - 2009

We were saddened by the passing of Dr Philip Poole-Wilson (British Heart Foundation Simon Marks Professor of Cardiology, Head of Cardiac Medicine at the National Heart & Lung Institute, Imperial College London, and Honorary Consultant Physician at the Royal Brompton & Harefield Hospitals) on March 4, 2009.

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The X Congress of the ISHR Chinese Section was held in Wenzhou, a famous commercial and seaside city of China, on Oct 20-24, 2008. The Congress was sponsored by the ISHR Chinese Section and the Cardiovascular Section of the Chinese Association of Pathophysiology. It was organized by the Wenzhou Medical College and Institute & Fu Wai Hospital, Chinese Academy of Medical Sciences. The Congress attracted 188 registrants, 42% of whom represented young scientists, including 48 students.

At the opening ceremony, Academician Han Qide, who is Vice Chairman of the Standing Committee of National People’s Congress of China, President of the China Association for Science and Technology, and Chairman of the International Association of Pathophysiology and Chinese Association of Pathophysiology, delivered warm welcoming remarks and an important speech. In his speech, Academician Han expressed his confidence in the future development of the ISHR Chinese Section and the Cardiovascular Section of the Chinese Association of Pathophysiology.

There were 5 plenary lectures given by specially-invited, outstanding international experts: Professor Metin Avkiran, Secretary General of the ISHR from King’s College London, UK; Professor Masatsugu Hori, Chairman of the upcoming XX ISHR World Congress from Osaka University, Japan; Professor John Y-J Shyy from the University of California, USA; Professor Hui Rutai from the Cardiovascular Institute & Fu Wai Hospital, Chinese Academy of Medical Sciences, and Professor Yu Xiyong, from the Guangdong Provincial People’s Hospital. During the 13 symposia of the Congress, 30 invited Chinese experts engaged in basic and clinical cardiovascular research delivered excellent lectures. Among these invited speakers were Professor Zhang Youyi, from Peking University Third Hospital, Professor Jin Huiming from Fudan University, Professor Li Xiaoying from PLA General Hospital, Professors Wu Liling and Zhu Yifrom Peking University Health Sciences Center, Professor Chen Qi from Nanjing Medical College, and Professor Yang Huangtian from Shanghai Institutes for Biological Sciences of the Chinese Academy of Sciences and Shanghai Jiao Tong University School of Medicine.

During the Congress, there was an amicable conversation between the leadership of the ISHR Chinese Section and Professors Avkiran and Hori. Academician Han, as the former Chairman of the ISHR Chinese Section, summed up the development of the section over the past several years. He expressed confidence that the Chinese Section will continue to support the ISHR and contribute to the cardiovascular research effort both nationally and internationally.

Finally, he happily introduced the new leadership of the ISHR Chinese section.

During the Congress, the participants submitted their research results, focusing on different aspects of cardiovascular physiology, pathophysiology, pharmacology and molecular biology, as well as on the clinical aspects of cardiovascular disease and translational medicine. A total of 236 abstracts were received and published in Acta Physiologica Sinica (Volume 60, Supplement 2, October 20, 2008). The papers presented at the Congress were outstanding, both qualitatively and quantitatively, with 91 oral presentations and 52 posters included in the symposia.

In the “How-to-Sessions”, Professors Tang, Chaoshu, a famous cardiovascular expert in China, and Wei Bin, an editorial director of Acta Physiologica Sinica, gave excellent speeches on how to select a research project and how to write a research thesis, respectively. All attendees enjoyed their wonderful talks.

A feature of this Congress was the extensive participation of young scientists and the high quality of their presentations. There were separate Selection Committees, appointed by the Scientific Program Committee, tasked with choosing the best oral and poster presentations. Narrowing the selection
to only a few awardees was difficult, with so many excellent young researchers presenting their work at this Congress. Finally, 9 best oral presentations and 9 best posters were chosen from among the young researchers. Xiao Han from Peking University Third Hospital was awarded first place among the oral presentations, and Huang Wei, from Guangdong Provincial People’s Hospital received the award for the best poster presentation. The awardees received a certificate and a cash prize during the closing ceremony.

During the Congress, the ISHR Chinese Section held an election. As a result, the Fifth Executive Committee of the ISHR Chinese Section was formed. Qide Han was elected as the Honorary Chairman of the Committee, Hui Rutai was elected as the Chairman of the Committee, Qi Chen, Youyi Zhang and Huangtian Yang were elected as the Vice-Chairpersons, Yi Zhu was elected as the Secretary, and Liling Wu was elected as the Treasurer. The Committee of the ISHR Chinese Section also revised the Section rules, with beneficial additions to enhance the development of translational medicine in cardiovascular diseases.

During the closing ceremony, Professor Youyi Zhang, Vice-Chairperson, introduced the new Committee members of the ISHR Chinese Section and extended thanks to Wenzhou Medical College for their successful organization of the meeting. The XI Congress of the ISHR Chinese Section will be held during the ISHR World Congress in Kyoto, Japan, in 2010.

We are looking forward to joining the 2010 World Congress in Kyoto!

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