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The New Team at JMCC

It is with great pleasure that I began my term as Editor in Chief of the Journal of Molecular and Cellular Cardiology (JMCC) in January 2008. I would like to begin by paying tribute to my predecessor, Dr Richard Walsh who has left the “yellow journal” in fine shape.

JMCC began under the editorship of Lionel Opie and Richard Bing in 1970 and was edited originally from Lionel’s small flat in London. It then moved across the Atlantic under the editorships of Arnold Katz, Norman Alpert and most recently Rick Walsh. Although the editorship may have returned to the UK, the JMCC remains truly international and covers a wide range of cardiovascular science as shown by the truly excellent and committed group of new Associate Editors.

The organization of JMCC has changed with the times. From its origins when letters were typed with carbon paper in the Opie flat (see JMCC 38, 539–40), it is now administered from San Diego and all manuscripts are transmitted electronically. The challenges have also changed. The ascendancy of the Impact Factor (IF) has increased the degree of competition between journals.

The new Editorial Team is committed to developing JMCC. We will strive for rapid decisions on submitted papers and publication of the highest quality original papers and review articles. Jointly with the ISHR (see box) we have initiated a prize for the best paper published by an early-career author. We see this as an important initiative to highlight the excellent science done by younger scientists.
Another new initiative is the introduction of a Point Counterpoint section. These articles will highlight controversial scientific questions and will be co-authored by two scientists who have opposite views on the question. Suggestions for issues and authors are welcomed and should be sent either to me (Eisner@man.ac.uk) or Don Bers (Associate Editor for Reviews; dmbers@ucdavis.edu; until April 1, 2008: dbers@lumc.edu).

Finally, the JMCC is very much the journal of the ISHR and I would be grateful for any comments you have concerning the journal either now or over the next few years.

David Eisner  D. Phil (Oxford, 1979). Currently British Heart Foundation Professor of Cardiac Physiology at the University of Manchester (U.K.). My research has concentrated on the control of intracellular ions in cardiac muscle. Recent work has concentrated on understanding how the size of the systolic Ca transient is controlled by the sarcoplasmic reticulum and (from a disease perspective) the link between calcium overload and cardiac arrhythmias.

Isabelle Baró Ph.D. (University College London, 1993). Currently CNRS senior researcher at the Institut du Thorax, Inserm U533 at the University of Nantes (France). My research has concentrated on the function and control of ion channels in the context of congenital cardiac arrhythmias and conduction defects. Recent work has concentrated on unveiling auxiliary proteins regulating trafficking and activity of the ion channels KvLQT1 and Nav1.5.

Donald M. Bers, Ph.D. (UCLA, 1978). Currently Professor and Chairman of the Dept. of Pharmacology, UC Davis School of Medicine. My research focus is on calcium and sodium regulation in cardiac myocytes. This includes fundamental studies of ion channels and transporters (sarcolemmal & sarcoplasmic reticulum), cellular integration and computational modeling, and Ca-dependent aspects of triggered arrhythmias and heart failure.

Keichi Fukuda, MD, PhD (Keio University School of Medicine, 1983). Currently Professor and Chief of Department of Regenerative Medicine and Advanced Cardiac Therapeutics, Keio University School of Medicine (Japan). My main research has focused on the stem cell biology and tissue engineering of heart regeneration. My recent work also investigated the molecular mechanism of physiological and pathophysiological cardiac sympathetic innervation and valvular heart disease.

W. Jonathan Lederer, M.D., Ph.D. (Yale; 1976, 1975). Currently Director of the Medical Biotechnology Center, University of Maryland Biotechnology Institute, Baltimore, MD, USA. Recent work focuses on cellular electrophysiology and on calcium signaling in heart cells in both the normal and diseased states at high temporal and spatial resolution.

Prof. Dr. med. Dr. h.c. Gerd Heusch, FRCP, Professor and Director of the Institute of Pathophysiology at the University of Essen Medical School, Germany. My research has focused on the control of coronary blood flow in health and disease and on myocardial ischemia/reperfusion. More recently, I am concerned with coronary microembolization and the role of mitochondrial connexin 43 in ischemia/reperfusion.

As part of the ongoing effort of the ISHR to promote young investigators and of JMCC to encourage first class submissions, we are delighted to announce a new, annual prize designed to recognize outstanding papers published by early-career authors in the *Journal of Molecular and Cellular Cardiology*. The prize (sponsored jointly by ISHR and the publisher, Elsevier) will consist of US $750 and a plaque. Two runners-up will receive $250 prizes. The winners and runners-up will be announced in the *JMCC* and the presentation will be made at the annual meeting of the ISHR section to which they belong.

Entries for the *JMCC* Young Authors Prize are invited from early-career scientists who are either the first or last author of a paper published in *JMCC* in a given year. Applicants must have received their research degree (MD, PhD or equivalent) less than 6 years before submitting the paper. In the case of candidates who have both an MD and a PhD degree, the date of the most recently awarded degree is the relevant one.

The first prize will be awarded for papers published in 2007 and authors will be contacted by email and asked to apply if appropriate. In future, candidates should check the appropriate box when submitting their manuscripts to *JMCC*.

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**ISHR-ES / SERVIER RESEARCH FELLOWSHIP 2008**

*Deadline for applications: March 31, 2008*

*For instructions and templates: [www.ishr-europe.org](http://www.ishr-europe.org)*
Allogeneic organ transplantation has assumed an essential role in today’s medicine. It can be life saving, and possesses an aura of romanticism because it involves exchange of vital organs between individuals, with the donor dead or alive. This applies particularly to transplantation of the heart, because of the mystery surrounding the heart for centuries. The way to successful allografts involved primarily overcoming graft rejection [transplantation immunity], while surgery offered relatively little technical obstacle. The breakthrough to clinical use of transplantation came with the serendipitous discovery of cyclosporin, the most powerful immunosuppressive compound yet known.

Eight Nobel prizes were awarded to workers in the field of transplantation, but none for the discovery of cyclosporin. The first Nobel in this field was given to Alexis Carrel in 1912 for his work on suturing vessels and for the transplantation of organs, including the heart. I was a research fellow with Carrel in the 1930’s at the Rockefeller Institute in New York and have referred to him as a brilliant investigator and a controversial individual, who moved to America from his native France. Carrel transplanted the heart of a donor dog into the neck of a recipient animal, creating an in situ Langendorff heart, a model which was later used to study the metabolism and the pathology of rejection. While many surgeons followed the procedure of Carrel, some attempted to create a preparation in which the donor heart assumed complete circulation in the recipient animal. We owe the technique of cardiac transplantation to the Stanford group under Norman Shumway. They had carried out meticulous tests on canines before they attempted transplantation on human patients. Prior to this, a human cardiac transplant by Christian Barnard had received much public attention.

The next recipients of the prize were Peter B. Medawar and Frank MacFarlan in 1960. Medawar was born in Rio de Janeiro in 1915 of Lebanese parents. The demonstration of acquired immunological tolerance and graft versus host reaction were Medawar’s greatest achievements; they were preceded by Ray Owen’s finding that twin cattle are born with, and retain through life, a stable mixture of each other’s red cells. In 1980, George Small, Jean Dausset and Baraj Benaceraff were the recipients of the award for their discovery of histocompatibility genes, a gene complex identified as HLA-2 and IR genes. Finally, in 1990 Joseph Murray and E. Donnall Thomas received the award for kidney and bone marrow transplantation in man.

Serendipity and persistence were responsible for the discovery of cyclosporin by the Sandoz Company in Basel, Switzerland. The pharmaceutical industry often employs methods which can be used routinely for large samples. This was fortunate, since in 1970 a systematic search for new antibiotics in soil samples collected in Norway and Wisconsin resulted in the discovery of a compound with disappointing antibiotic properties, but with immunosuppressive activity. It was discovered that the compound reduced the hemagglutinin titer of sera of mice that had been immunized with sheep erythrocytes. A fungus was found to be responsible and its immunosuppressive action was later confirmed. The Sandoz worker showed that it inhibited immunocompetent lymphocytes in a reversible manner and called the compound cyclosporin because they found it to be a cyclic peptide which occurs in the spores and possesses strong immunosuppressive activity. But there still was doubt at Sandoz on its future use, because transplantation at that time was not a high priority. Rather, it was thought that the compound could be of greater use in inhibiting chronic inflammation. In addition, the first pharmacokinetic trials in man with cyclosporin were negative, stopping all work, until in 1973 senior investigators at Sandoz volunteered to swallow the drug in various solutions. They found that cyclosporin resulted in considerable inhibitory activity for mouse lymphocytes. In 1977, the first publication on patients appeared and the results were presented to the British Society of Immunology. Also in 1977, cyclosporin was first used in patients and the clinical results were published in the Lancet; however, the use of cyclosporine remained controversial because of the high incidence of lymphomas. Lowering the dose saved cyclosporin for future clinical use. Both H. Stahelin and J. F. Borel were involved in the initial work on cyclosporin. Novartis, which took over Sandoz, initiated a careful examination which gave Stahelin the nod of priority.

Borel ended his report on the history of cyclosporin, quoting Harry Truman, “It is amazing what can be accomplished if you don’t care who gets the credit”. And Stahelin wrote, “The prehistory and history of cyclosporin are a good example to show that pharmaceutical research (continued on page 8)
As you know, one of the goals of our Society is to recognize and encourage scientific excellence by presenting awards to individuals who have distinguished themselves for their contributions to our understanding of cardiovascular biology and pathophysiology. For many years, the ISHR has bestowed a number of prestigious (and highly coveted) awards to scientists all over the world. These recognitions are a vital part of our activities and serve multifarious purposes. They do much more than honoring outstanding scholars with a deserved reward. They help to define our own identity and values as a Society. They send an unmistakable signal that we place great value on excellence in cardiovascular research. They improve the quality of our meetings by bringing outstanding investigators and speakers into the program. And they promote wider interest in our Society among the leaders in cardiovascular science.

To further enhance these programs, the International Section has recently revised our portfolio of awards. Below I summarize the salient changes:

1. Creation of the **ISHR Distinguished Leader Award**. The purpose of this new award is to recognize individuals who have made sustained and outstanding contributions to accomplishing the mission and advancing the objectives of the ISHR. Research achievements will not be a major factor (these are already covered by our existing awards). The recipient will be selected on the basis of a distinguished and consistent track record of major contributions to the Society (the time element should be noted: the duration and consistency of the service will be as important as its quality). The background to this initiative is that, while there already several mechanisms to honor scientific achievements through our existing awards, the Society does very little to recognize outstanding leadership. There are volunteers who have selflessly devoted much time and effort to our Society over a period of many years, bringing about changes that have benefited the entire organization and, in many cases, are not widely appreciated among the membership of the ISHR. It is hoped that the DLA will help give the proper credit to these outstanding individuals.

   Winners will receive a medal and a $1,000 honorarium; their photograph and biosketch will be published in *Heart News and Views* and posted on the ISHR website. This will be an annual award; in non-Congress years, the winner will be recognized at the meeting of the Section to which he/she belongs. For further details, please visit the ISHR website at [www.ISHRworld.org](http://www.ISHRworld.org).

2. The **Outstanding Investigator Award**, which heretofore was bestowed only in non-Congress years, will now be bestowed every year, including the Congress years. This increased regularity of the OIA will hopefully lessen some confusion regarding the ISHR awards.

3. We have rescinded the previously-stipulated age limit of 55 years for the **Research Achievement Award**. We felt that this may at times be restrictive, and that using “career age” rather than “biological age” would be more appropriate. In our new guidelines, we indicate that the three research awards of the ISHR (Outstanding Investigator Award, Research Achievement Award, and Harris Distinguished Scientist Award) are targeted at subsequent stages in the career of an investigator, as a continuum from the most junior stage (OIA) to the most senior stage (Harris). Specifically, the OIA recognizes established investigators who have reached independence, have already made important scientific discoveries, and lead a growing research program that is likely to play a major role in the future; these individuals are expected to be more junior than those receiving the RAA and Harris awards. Both the RAA and the Harris Award recognize senior scientists who have a distinguished track record of innovative scientific contributions that have had a major impact on our understanding and/or treatment of cardiovascular disease. The difference between the two is that, unlike the RAA, the Harris Award is a lifetime recognition; it is intended for senior investigators with a long and consistent track record of excellence. Although no formal age limits are stipulated, it would normally be expected that
the recipient of the RAA be at least 50 years old, and that of the Harris Award at least 60 years old. In general, the OIA is targeted at Assistant or Associate Professors (or equivalent), while the RAA and Harris awards are targeted at full Professors (or equivalent).

4. Rotation of the Distinguished Lectures. In order to better distribute the benefits of the ISHR Distinguished Lectures (Reimer, Pfeffer and President’s) within the Society, Council decided last June to adopt a scheme whereby these Lectures will rotate among the three major Sections (European, Japanese, and North American) in non-Congress years, with each Section hosting one of the three lectures in a given year. (In Congress years, all three Lectures will be held at the Congress site.) The speakers, however, are selected from the entire membership of the Society. This new system will also have the advantage of fostering closer collaboration among Sections and between regional Sections and the International Section, since the lectures will be sponsored by the International Section and speakers from one Section will be invited to meetings of another Section. Such a strategy is consonant with our fundamental goal of fostering the cohesiveness of the Society. As I wrote in this column before, the ISHR is one organization, not a conglomerate of seven different Sections.

Other than for the rotation among Sections, the stipulations for the three Distinguished Lectures will not change, and neither will those for the Bing Award for Young Investigators. The Table below provides a quick summary of the updated ISHR awards; this table with appropriate links to detailed descriptions of the ISHR awards can also be found at www.usouthal.edu/ishr/awards/ishrawards2007.htm.

We are very proud of our award portfolio. The ISHR offers a superb selection of honors that encompasses the entire spectrum of the scientific cardiovascular community, from the very early stages to the most senior levels. We now have three major scientific awards of great international renown (each targeted at a different level of seniority), three major lectures (each targeted at a different research field), a coveted young investigator award for which applicants compete from all over the world, and a prestigious leadership award. All of these awards have been carefully designed to ensure that our portfolio is complete while avoiding redundancy. Furthermore, the process for selecting recipients is as rigorous and fair as that of any Society I am aware of.

As a history buff, I always like to look at things from a historical perspective. When I became Secretary General in 1998, the ISHR had only the Bing and Harris awards and no lectures. Ten years later, we boast five awards and three lectures, all of which have a high profile. In a short time, we have gone from 2 to 8 honorific and internationally coveted recognitions. This is what I would call real growth. The remarkable changes in our award portfolio tell us that we can improve our society if we work at it.

I believe that these changes significantly enhance our award program and advance our mission. As always, I welcome your feedback and comments.

Roberto Bolli, M.D.
President, ISHR

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<th>Award:</th>
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<td>Notes:</td>
<td>Young Investigator Award competitions are also held annually at Section Meetings</td>
<td>Three Distinguished Lecture Awards (Reimer, Pfeffer and President’s) cover distinct areas of investigation</td>
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**RICHARD BING AWARD** *(early career investigators)*

The purpose of the Richard J. Bing Award for Young Investigators is to recognize outstanding endeavors by new investigators and to encourage continued biomedical research careers broadly related to cardiovascular biology. The Award is bestowed triennially during the ISHR World Congress. Four finalists are selected by a Committee of the ISHR for presentation of their work at the World Congress. The winner will receive a plaque and a cash award of US $5,000. The three runner-ups will receive a plaque and a $1,000 honorarium.

**KEITH REIMER DISTINGUISHED LECTURE**

This lecture will be held at each World Congress of the ISHR and, in non-Congress years, at the annual meeting of one of the three largest ISHR Sections on a rotating basis. The lecture is intended to be a high profile event and will be scheduled as a keynote plenary lecture. The International Council will select the speaker. **The topic of the lecture will be in the field of molecular or cellular biology, genetics, genomics or proteomics, with a content that is of broad interest to the cardiovascular community.** The speaker will be reimbursed for travel expenses, and will receive a plaque and a $1,000 honorarium.

**JANICE PFIEFFER DISTINGUISHED LECTURE**

This lecture will be held at each World Congress of the ISHR and, in non-Congress years, at the annual meeting of one of the three largest ISHR Sections on a rotating basis. The lecture is intended to be a high profile event and will be scheduled as a keynote plenary lecture. The International Council will select the speaker. **The topic of the lecture will be in the field of ischemia, coronary hemodynamics, vascular biology, cardiac metabolism, or contractile mechanisms but the content should be chosen to be of broad interest to the cardiovascular community.** The speaker will be reimbursed for travel expenses, and will receive a plaque and a $1,000 honorarium.

**THE PRESIDENT’S LECTURE**

This lecture will be held at each World Congress of the ISHR and, in non-Congress years, at the annual meeting of one of the three largest ISHR Sections on a rotating basis. The lecture is intended to be a high profile event and will be scheduled as a keynote plenary lecture. The International Council will select the speaker. **The topic of the lecture will be in the field of molecular or cellular biology, genetics, genomics or proteomics, with a content that is of broad interest to the cardiovascular community.** The speaker will be reimbursed for travel expenses, and will receive a plaque and a $1,000 honorarium.

**OUTSTANDING INVESTIGATOR AWARD** *(established investigators)*

The purpose of this annual award is to recognize an established investigator who has reached independence, has already made important scientific discoveries, and leads a growing research program likely to play a major role in the future. The main criteria for selecting awardees are scientific excellence, independence, and potential for future research contributions. While the Peter Harris Award recognizes lifelong accomplishments and the Richard Bing Award recognizes young investigators, the Outstanding Investigator Award is targeted at investigators who are in the intermediate phase of their academic career. These individuals are expected to be more junior than those receiving the RAA and Harris Awards; in general, this award is targeted at Assistant or Associate Professors (or equivalent). The winner will deliver a major lecture and will receive a plaque and an honorarium of $5,000.

**RESEARCH ACHIEVEMENT AWARD** *(established senior investigators)*

The purpose of this Award is to recognize outstanding scientists who have a distinguished track record of innovative scientific contributions that have had a major impact on our understanding and/or treatment of cardiovascular disease, and who are likely to continue to make major contributions in the future. Although no formal age limit is stipulated, it would normally be expected that the recipient of the RAA be at least 50 years old. This is a very distinguished Award of international importance that is bestowed triennially during the ISHR World Congress. The winner will present a major lecture and will receive a plaque. The monetary prize for the Research Achievement Award is $20,000.

**PETER HARRIS DISTINGUISHED SCIENTIST AWARD** *(lifetime research achievement)*

The purpose of this award is to recognize outstanding scientists who have a long and distinguished track record of innovative scientific contributions that have had a major impact on our understanding and/or treatment of cardiovascular disease. With the inauguration of the Research Achievement Award (RAA), the Peter Harris Award has been focused to recognize and reward lifetime contributions to science. Although no formal age limit is stipulated, it would normally be expected that the recipient of the Peter Harris Award be at least 60 years old. Like the RAA, this is a very distinguished Award of international importance that is bestowed triennially during the ISHR World Congress. The winner will present a major lecture and receive a plaque and an honorarium of $5,000.

**THE ISHR DISTINGUISHED LEADER AWARD** *(illustrious service to the ISHR)*

Created in 2007, the Distinguished Leader Award is a prestigious award that is conferred annually to an individual who has made sustained outstanding contributions to accomplishing the mission and advancing the objectives of the ISHR. Candidates will be nominated by each Section President and the President of the International ISHR, and the winner will be selected by the International Council. In non-Congress years, the award will be presented at the meeting of the Section to which the recipient belongs. The winner will be reimbursed for travel expenses, and will receive a plaque and a $1,000 monetary prize.
REPORT ON THE XVI MEETING OF THE LATIN AMERICAN SECTION
(SEPTEMBER 8, 2007; SAO PAULO, BRAZIL)

The 16th Meeting of the International Society for Heart Research – Latin American Section was held in São Paulo, Brazil, on September 8, during the 62nd Congress of the Brazilian Society of Cardiology. The opening lecture by Dr Francisco RM Laurindo (São Paulo – Brazil) was titled, “Oxidative stress: a redefinition of concepts, mechanisms and therapeutic implications”. Dr Laurindo pointed out that redox-dependent signaling in vascular cells is dependent on the generation of reactive oxygen species by enzymes such as NADPH oxidase complex. Recent evidence indicates that the endoplasmic reticulum redox chaperone protein disulfide isomerase associates with and assists NADPH oxidase activity and provides a subcellular link between endoplasmic reticulum stress and oxidative stress. This connection appears to be involved in the genesis of several diseases, including diabetes, atherosclerosis, and cardiac hypertrophy.

A Symposium on “Oxidative stress in cardiovascular diseases: mechanisms and clinical implications” was coordinated by Dr Laurindo and included the following lectures: (1) “Oxidative stress in Hypertension”; Dr José Geraldo Mill (Espírito Santo – Brazil) presented a brief review of recent data relating oxidative stress and hypertension, with emphasis on the possible contribution of oxygen free radicals for endothelial dysfunction in this disease. (2) “Role played by mitochondrial dysfunction in cellular aging and ischemia”; Dr Alicia J Ko-waltowski (São Paulo – Brazil) showed that mild mitochondrial uncoupling and calorie restriction show the same physiological, redox, and life span effects. (3) “Toll-like 4 receptor and atherosclerosis”; Heraldo Possolo de Souza (São Paulo – Brazil) discussed the importance of Toll-like 4 receptor in atherosclerosis. The controversies regarding this subject were summarized and evidence suggested that the knockdown of Toll-like 4 receptor protected against cellular activation in atherosclerosis in LDL receptor of (-/-) mice.

This symposium was followed by a lecture presented by Dr Alberto Crottogini (Buenos Aires - Argentina) and coordinated by Dr Paulo Tucci (São Paulo – Brazil) that addressed “Vascular endothelial growth factor (VEGF) and cardiac regeneration”. Dr Crottogini presented evidence that vascular endothelial growth factor gene transfer in porcine and ovine models of myocardial ischemia and infarction induces angiogenesis, arteriolar growth and cardiomyocyte hyperplasia, resulting in improved myocardial perfusion, reduced infarct size, and improvement of global and regional left ventricular function.

Thereafter, a symposium was held on “Intracellular Ca²⁺ signaling in Cardiac

THERE AT THE TRANSPLANTATION OF THE HEART
(continued from page 4)

quite often proceeds in a path with many windings and they illustrate how people, groups of people, strokes of luck, serendipity, preceding events, etc. contribute to research endeavors of this kind and that there are those factors which make the difference between the usual frequent failures and the rare success”.

References


Carrel A. Results of the transplantation of blood vessels, organs and limbs. JAMA 1908; 51: 1662-1667.

Carrel A. Results of the transplantation of blood vessels, organs and limbs. JAMA 1908; 51: 1662-1667.


Richard J. Bing, M.D.
Diseases’. The symposium was chaired by Dr Alicia Mattiazzi (La Plata – Argentina) and Dr Gina Sanchez (Santiago – Chile) and focused on new exciting findings in this central area of calcium cycling in health and disease. Dr Rosana Bassani (Campinas – Brazil) talked about “Changes in Ca2+ handling in ventricular myocytes under pressure overload” showing that enhanced contribution of the sarcoplasmic reticulum-dependent calcium fluxes to excitation-contraction coupling and relaxation is proposed to represent an endogenous, adaptive mechanism that allows maintenance of contractile activity and greater responsiveness to beta-adrenergic stimulation observed during acute and chronic hypertension. Dr Margarita Salas (La Plata – Argentina) presented the topic “CaMKII: an apoptotic signal in ischemia-reperfusion injury”. Dr Salas presented results suggesting a dual effect of the activation of this kinase in the I/R injury. In the stunned heart produced by reversible I/R injury, CaMKII activation induces a beneficial cascade involving the phosphorylation of Thr17 site of PLN, improving Ca handling by SR and ameliorating the depressed contractility. In the irreversible I/R injury the effect of the activation of this kinase would initiate a detrimental cascade which would involve SR Ca overload and possibly mitochondria, leading to apoptosis and necrosis. The subject “Modulation of cardiac ryanodine receptors (RyR) activity by Reactive Oxygen Species” was developed by Dr Paulina Donoso (Santiago – Chile). Data were presented showing that the activation of NADPH oxidase by exercise or tachycardia generates reactive oxygen species in the vicinity of RyRs; as a consequence RyRs are S-glutathionylated and their activity increases. Finally, Dr Irene Ennis (La Plata - Argentina) reported on “NHE inhibition induced-cardiac hypertrophy regression: The Role of Calcineurin-NFAT Pathway” and presented results showing that the regression of cardiac hypertrophy caused by NHE-1 inhibition, which is independent from any change in blood pressure, is accompanied by normalization of the calcineurin/NFAT pathway. All speakers presented new results that generated interesting debates and friendly discussions.

At night, a dinner brought the members together to celebrate the success of the meeting and to enjoy typical Brazilian cuisine and delicious Argentinean and Chilean wines.

Rossana A. Bassani (Campinas, Brazil), Lea M. D. Delbridge (Melbourne, Australia) and Alicia Mattiazzi (La Plata, Argentina) enjoying a dinner on the evening of the Symposium.
News from the Australasian Section

For the Australasian Section it has been a very full year of science in 2007. Following on soon after our major involvement at the Bologna Congress in June, many of our members also made the trip across the Tasman to join with our colleagues of the Cardiac Society of Australia and New Zealand in Christchurch for a most successful meeting in August. Both events have been acclaimed as calendar highlights by our members this year. In Bologna, the science and culture, the hospitality and the climate were all outstanding. We congratulate Roberto Ferrari and his organisation team for staging such a memorable event. Our Section’s commitment to the program was evidenced by the very good attendance of members from the southern hemisphere. It was particularly pleasing for the Section to be able to provide support for a relatively large number of early-career investigators to attend, and to see the energy with which these young scientists engaged in the events of the Congress—and even mounted their own symposium.

In Christchurch, one of our tasks was to do our Section housekeeping. It was pleasing to have a well attended Annual General Meeting to review the year and to consider the appointment of our new Australasian Section Council for the 2007-2010 triennium. The appointment of all nominees for the new council was unanimously endorsed – Lea Delbridge has been elected as the new President, supported by David Saint who takes on the role of Secretary. The new Council has been modeled to include more specific ‘portfolio’ responsibilities for members, and we will be developing this concept further. Joining us on Council are a number of new members including Julie McMullen (Vic), Len Arnolda (WA), Peter McLennan (NSW), Marie Ward (NZ), Hung Fat Tse (HK) and Vennetia Danes (Indonesia).

In welcoming new Council members, it was also timely to express our appreciation for the contributions of those who have been active on the outgoing Council: Sal Pepe, Xiao Jun Du, Helen Kiriazis, John Headrick, Marie Bogeyevitch, Bruce Smail, Kate Huggins and Iwan Williams.

We certainly hope to enjoy the ongoing active involvement of these colleagues beyond their recently completed Council terms. In particular, the major contribution made by Sal Pepe in the role of President over the last few years deserves special recognition. At the AGM, the membership took the opportunity to express their appreciation of Sal’s efforts and commitment. Sal now takes on the mantle of ‘immediate past president’, and we look forward to his continuing investment in the Society.

An important aspect of any scientific society is the support and assistance it offers to its student members. ISHR has always encouraged students to present...
their work at Congresses and local meetings. For many students, this is their first opportunity to interact with other researchers outside of their own academic institution. A highlight of the Christchurch meeting was the hotly contested Student Investigator Prize. This year the Prize money was increased to $1000 for the winner, with awards of $500 each for the two runners-up.

The first of the three presentations was from Karen Lu Fang, of the Baker Heart Research Institute. Her talk, entitled “Extracellular matrix remodeling in a model of dilated cardiomyopathy” outlined some of the complex changes that occur to the extracellular matrix in relation to the progression of dilated cardiomyopathy. Another of the contestants was Christine Ball, from the University of Adelaide, with her talk entitled “Heterogeneity in vasomotor responses to L- and T-type calcium channel blockers”. Christine gave an interesting talk in which she compared the contractile responses of large and small blood vessels exposed to mibefradil. Both Lu, and Christine, spoke confidently about their projects, and presented a large body of work in their talks. Kimberley Mellor (University of Melbourne), with her talk entitled “A high fructose diet induces myocardial oxidative stress but not hypertension in mice”, impressed the judges with the clarity of her presentation, her timing, and her enthusiasm for her project and the judges were unanimous in declaring her the winner. All three of the contestants are congratulated on the very high standard of their presentations. They are all currently in the midst of their PhD studies, and we look forward to many more presentations from them at future ISHR meetings.

Lea Delbridge, President (University of Melbourne) and Marie Ward, Council Member (University of Auckland)

Join us at the 2008 ISHR AUS-Section Meeting
August 7-10, 2008
Adelaide Convention Center

The program of this joint meeting with the Cardiac Society of Australia and New Zealand will cover a wide range of basic science and clinical areas of interest.

Details can be found at: www.sapmea.asn.au/conventions/csanz2008/index.html
MARTIN LOHSE studied medicine and philosophy in Göttingen, London and Paris. He did his doctoral thesis in neurobiology at the Max-Planck-Institute for Biophysical Chemistry (director Otto Creutzfeldt) in Göttingen (1981). Following his postdoctoral years with Ulrich Schwabe in the Pharmacological Institute of the University of Heidelberg (1983-7) he joined the group of Robert Lefkowitz at the Howard Hughes Medical Institute, Duke University, Durham, NC, USA. He became an assistant medical research professor at Duke University in 1990. From the end of 1990 to 1993 he was a group leader at the Laboratory of Molecular Biology of the University of Munich / Max-Planck-Institute of Biochemistry in Martinsried, Germany, and in 1993 he moved to his current position as Chairman of the Institute of Pharmacology and Toxicology at the University of Würzburg. In 2001 he also became the Founding Director of the Rudolf-Virchow-Center/DFG-Research Center for Experimental Biomedicine, one of the first three national Centers of Excellence funded by the German Research Council (DFG).

Dr. Lohse’s research focuses on cell surface receptors and their mediators, and on the biochemical and physiological signals that they produce. His most important contributions include the discovery of a key mechanism that switches off receptors and its critical role in heart failure, the development of several receptor-selective ligands, and the development of technologies that permit the visualization of receptor activation and signaling in living cells.

During his years in Heidelberg, he investigated receptors for adenosine, a prototypical family of G-protein coupled receptors that mediate, among other functions, inhibition of neurotransmitter release, control of cardiac function and vasodilatation. This work led to the development of several highly selective adenosine receptor ligands that proved useful for an array of pharmacological and biochemical studies. For example, they permitted the study of A1-receptors in the heart as well as the characterization and partial purification of A2-receptors in the brain and in platelets. Studies with new UV-sensitive radioligands allowed the first identification of these receptors by photoaffinity labeling.

Martin Lohse’s subsequent investigations with Robert Lefkowitz were concerned with the dynamic regulation of receptors. These studies led to the discovery of β-arrestin, a protein that binds to and thereby desensitizes many G-protein coupled receptors. Such desensitization was found to proceed as a two-step mechanism: First, activated receptors are phosphorylated by a family of kinases called G-protein coupled receptor kinases (GRKs), and second, β-arrestins bind to the phosphorylated receptors. This mechanism appears to be responsible for the loss of effects of many drugs that activate receptors, such as opiates and antiasthmatic β-receptor agonists.

Martin Lohse’s group in Munich then discovered that this mechanism is highly active in failing hearts, and that this may be a key factor in a vicious circle of loss of cardiac responsiveness and increased activity of sympathetic nerves. Various transgenic models led to the identification of mechanisms that link chronic stimulation of the cardiac adrenergic receptors to structural and functional damage of the heart. Several such mechanisms were discovered that appear to be critical for the development of heart failure. These discoveries provide a rationale for the treatment of heart failure with β-blockers, and they may also pave the way for new treatment strategies.

In recent years, Martin Lohse and his group have been developing technologies to visualize receptor activation and signaling in living cells. These studies are based on the design of fluorescently labeled receptors and signaling proteins and provide the means to see entire signaling cascades under the microscope. The transfer of these technologies into transgenic models now provides a new way to study receptor signaling in vivo. They demonstrate that receptor signals in a cell can show dramatic changes in space and time. Receptors may thus excite an entire cell or only small regions, and the signals can be steady or rapidly oscillating.

Martin Lohse has received numerous awards and is member of many scientific societies. He was the recipient of the Leibniz Award of the German Research Foundation, of the Ernst-Jung Prize for Medicine, and he is a member of the Leopoldina German Academy of Sciences and the Bavarian Academy of Sciences. He is the author of more than 200 peer-reviewed publications, and many of these have been quoted several hundred times. He is the mentor of many scientists who have then established their own laboratories and have become professors in universities all over the world. For many years he has served on a large number of committees and advisory boards, both in Germany and internationally. Among other duties, he is the director of the International Graduate School of the University of Würzburg, a member of the Senate of the German Research Council (DFG) and of the National Ethics Council.
It was a great honour to be awarded the ISHR-ES/SERVIER Research Fellowship in 2006, and I am pleased to present a summary of my ongoing research project. A study published by the president of the ISHR European Section, Professor Fabio Di Lisa in 2001, first provided the initial inspiration for my PhD research project, which explored the role of the mitochondrial permeability transition pore (mPTP) in cardioprotection. I began my PhD research mid-way through my clinical Cardiology training at the Hatter Cardiovascular Institute, University College London, from 2001 to 2004 under the supervision of Professor Derek Yellon. My post-doctoral research has focused on examining the interplay between certain pro-survival kinases such as Akt and Erk1/2 and the mPTP, and investigating the contribution of these two components to a common cardioprotective pathway recruited at the time of myocardial reperfusion by both ischaemic preconditioning and postconditioning.

The mPTP and the RISK pathway in cardioprotection
The mPTP is a non-selective high-conductance channel which forms in the inner mitochondrial membrane in response to mitochondrial calcium and phosphate accumulation, oxidative stress, and ATP depletion; conditions which exist in the first few minutes of myocardial reperfusion. Its opening at the onset of myocardial reperfusion mediates cardiomyocyte death by uncoupling oxidative phosphorylation leading to ATP depletion and causing mitochondrial matrix swelling. We found that preventing its opening during the first few minutes of myocardial reperfusion using known mPTP inhibitors such as ciclosporin-A (CsA) and sanglifehrin-A (SfA) reduced myocardial infarct size in experimental animal models and improved post-ischaemic contractile function in human atrial trabeculae harvested from patients undergoing cardiac surgery. Crucially, it transpires that mPTP inhibition at the point of myocardial reperfusion underlies the cardioprotection elicited by the endogenous phenomena of ischaemic preconditioning (IPC) and post-ischaemic contractile function in human atrial trabeculae harvested from patients undergoing cardiac surgery. Crucially, it transpires that mPTP inhibition at the point of myocardial reperfusion underlies the cardioprotection elicited by the endogenous phenomena of ischaemic preconditioning (IPC) and post-ischaemic contractile function in human atrial trabeculae harvested from patients undergoing cardiac surgery. My post-doctoral work has been investigating the mechanism through which IPC and IPost exert their inhibitory effect on the mPTP, and in this regard I have focused on the role of certain pro-survival kinases which we have termed the reperfusion injury salvage kinase (RISK) pathway, as a potential link to the mPTP.

Linking the RISK pathway to the mPTP
The RISK pathway refers to a group of pro-survival protein kinases such as Akt, Erk1/2 and PKC, which have the ability to limit myocardial infarct size, on activation by a diverse array of pharmacological agents, at the time of myocardial reperfusion. Of critical importance, we have been able to demonstrate that both IPC and IPost elicit their infarct-limiting effects in part through activation of the RISK pathway, which in turn limits mPTP opening.
effects through the activation of the RISK pathway, shifting the focus to the myocardial reperfusion phase as a target for cardioprotection. In this regard, we have also found that conventional signalling preconditioning mediators such as reactive oxygen species, PKC and the mitochondrial KATP channel, are required at the time of myocardial reperfusion in preconditioned rat hearts\textsuperscript{12}. Furthermore, in order to translate these findings into the clinical setting, it was essential to determine whether the RISK pathway confers cardioprotection in human myocardial tissue (see below). In this respect, we have demonstrated that the activation of the RISK pathway at the time of myocardial reperfusion using either erythropoietin\textsuperscript{13} or ischaemic post–conditioning\textsuperscript{14}, improved recovery of contractile function in hypoxic human atrial trabeculae harvested from patients at the time of cardiac surgery.

Having implicated both the RISK pathway and the mPTP in cardio–protection, the next aim was to determine whether these two components were linked. In this regard, we have demonstrated that activating the RISK pathway using various pharmacological agents such as metformin (Fig. 1)\textsuperscript{15} and visfatin (ISHR abstract 2007) have the capacity to reduce myocardial infarct size in animal models and inhibit mPTP opening in isolated cardiomyocytes. We have been able to provide direct evidence linking Akt phosphorylation with mPTP inhibition in a study in which HL–1 cells (a murine atrial–derived cardiac cell line) that had been transfected with a constitutively–active Akt gene construct were more resistant to mPTP opening provoked by oxidative stress compared to cells transfected with an empty vector\textsuperscript{16}.

**Mitochondrial dynamics**

During the course of my Research Fellowship I was fortunate to have the opportunity to spend 3 wintry months in the beautiful University City of Padova at the Venetian Institute of Molecular
Medicine in collaboration with Prof Luca Scorrano, who is a leading expert in the exciting field of mitochondrial dynamics. Mitochondria are dynamic organelles which possess the ability to change their morphology between an elongated tubular interconnected network (a process called mitochondrial fusion) and a fragmented discrete punctiform structure (a process called mitochondrial fission) (Fig. 2). Of direct relevance to my own research interest, it transpires that cells destined for apoptotic cell death fragment their mitochondria13. Furthermore, the process of mitochondrial fragmentation predisposes to mPTP opening. I was therefore keen to explore the role of RISK pathway activation on mitochondrial dynamics with the current working hypothesis being that the activation of Akt exerts its cardioprotective effect by inhibiting mitochondrial fragmentation, thereby preventing mPTP opening. Preliminary data suggests that the over-expression of Akt is capable of inhibiting mitochondrial fragmentation (AHA Abstract 2007), and our next step will be to examine this process in the context of cardioprotection.

Translational clinical studies
Being a Clinician Scientist, the translation of findings made in the basic science laboratory into the clinical setting for patient benefit remains my key objective (Fig. 3). In this regard, we have recently demonstrated that remote ischaemic preconditioning (RIPC), using transient arm ischaemia applied non-invasively with a blood pressure cuff, is capable of reducing myocardial injury sustained by patients undergoing elective cardiac surgery18. We are currently investigating whether RIPC using limbischaemiaexerts its cardioprotective effects through the RISK-mPTP pathway. We also intend to examine whether remote ischaemic postconditioning, in which the preconditioning limb ischaemia is applied after the onset of acute myocardial ischaemia, has the capacity to reduce myocardial injury in patients presenting with an acute myocardial infarction.

Finally, we are currently investigating whether pharmacological agents which are already in clinical use, such as erythropoietin, atorvastatin, and ciclosporin-A, and which are known to activate the RISK pathway and inhibit mPTP opening, are capable of conferring cardioprotection in patients undergoing cardiac surgery and in patients presenting with an acute myocardial infarction.

References

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