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**CINCINNATI: MEETING IN THE HEARTLAND**

**REPORT FROM THE XXX NORTH AMERICAN SECTION MEETING (JUNE 17-20, 2008)**

How appropriate for the 30th ISHR North American Section meeting to be held in Cincinnati, Ohio, the “heart” of the midwestern United States. While in town, attendees enjoyed not only an outstanding meeting program but also great weather, which is unusual for humid Cincinnati in the summer. The meeting was hosted by Cincinnati Children’s Hospital Medical Center and the University of Cincinnati College of Medicine at the Hilton Cincinnati Netherland Plaza. The venue is a National Historical Landmark known for its French art deco, and provided the meeting with beautiful ambiance and fine dining during the interactive breaks and social hours throughout the meeting.

The meeting was attended by approximately 350 scientists and physicians representing fourteen countries, from Japan to Canada, spanning five continents. Organizers Jeffrey Robbins and Litsa Kranias formulated a schedule packed with morning and afternoon plenary sessions, afternoon poster sessions, and lunches...
The meeting program not only included excellent presentations by accomplished and well-established scientists, but also paid special tribute to the achievements of young scientists. Indeed, the conference was well-attended by graduate students, post-doctoral fellows and junior faculty. Notably, travel awards were presented to C. Schmidt (University of Guelph), D. Torres (University Hospital of Palermo), C. L. Stables (King’s College) and R. Ujwal (UCLA) who, along with other young investigators, presented their work at the poster sessions where a total of 96 posters were presented. The hotel personnel continuously provided the presenters and attendees with hors d’oeuvres and beverages and the atmosphere was friendly and relaxed, providing the opportunity for investigators to freely discuss their findings and possible future research directions.

A highlight of the meeting was the Young Investigator Competition. Six finalists, Quinghang Liu (Cincinnati Children’s Hospital Medical Center), Gang Lu (UCLA), Scott MacDonnell (Temple University), Kensuke Noma (Brigham & Women’s Hospital Harvard Medical School), Patrick Yue (Stanford University), and Yiqiang Zhang (Heart Institute Cedars-Sinai Medical Center) presented their extensive and innovative work on a diverse set of topics. The judges (Mark Sussman, Tish Murphy, Paul Simpson, Tom Force, and Wally Koch) had a difficult time choosing a winner from among this talented group of young scientists, and in the end Don Bers presented a first place prize to two individuals, Scott MacDonnell and Gang Lu. Scott MacDonnell presented work on the negative regulation of NFAT translocation by CaMKII, while Gang Lu discussed his findings on PP2Ce as a novel phosphatase involved in ER stress regulation and calcium cycling.

Another young researcher, Alok Pachori, was awarded the first annual JMCC Early-Career Authors Prize by the ISHR and the Journal of Molecular and Cellular Cardiology (JMCC) for his productive and innovative work on heme-oxygenase-1-induced cardioprotection against hypoxia/reoxygenation.

Of special interest, a representative from the NIH Heart and Lung Institute discussed funding opportunities and the...
Institute’s current interests and directions. The discussion was not only informative to young investigators but also benefited the senior investigators. This is just another example of the wonderful balance achieved at this meeting between events featuring and catering to young and established investigators.

Meeting organizers Jeff Robbins and Litsa Kranias take a well-deserved break to celebrate the successful meeting.

Notably, the meeting was also characterized by numerous social gatherings. These events, including the welcome ceremony and the banquet, were held in the elegantly-decorated Hall of Mirrors. The food was excellent and the wine ample creating a perfect atmosphere for the attendees to discuss their research interests, freely exchange ideas, form meaningful collaborations and just enjoy catching up with an old or new friend.

Reviews of the meeting were very positive with an abundance of praise bestowed upon the organizers. Indeed, Litsa Kranias and Jeff Robbins put together a wonderful program at a beautiful location to make this year’s North American Section meeting memorable. Next year’s annual meeting is organized by Meredith Bond, William Stanley, Mandeep Mehra, Tish Murphy, Brian O’Rourke and David Kass and will be held in Baltimore on May 26-29 at the Marriott Waterfront. The topic will be “New Discoveries for Prevention and Treatment of Heart Disease” and the meeting promises to be as informative, interesting and enjoyable as the one in Cincinnati. We hope to see you there!

Tracy Pritchard
Persoulla Nicolaou
University of Cincinnati
It has been said that it is more rewarding to strive than to arrive. We in the medical sciences are rewarded by exploring the secrets of nature. When we finally reach our goal, we discover that the road does not end, but leads beyond the horizon to another distant yet unexplored goal. In this essay, the reader will forgive me when I neglect matters of the heart and tell of the fight against another menace to mankind: malignant growth. I feel persuaded to do so because the work is relevant to cardiac research and great men have made great history in this field. Whatever field of medical science we deal with, it is the individual who breaks through barriers of tradition to discover new territories.

For the last century, there has been a public demand for the eradication of cancer. It was thought that cancer had only one cause and therefore only one treatment. But no amount of funding or publicity could find the magic wand to discover a specific cure. Only in the past thirty years has molecular biology taught us that cancers are separate biological entities and therefore require different approaches. In the early 1970’s, Judah Folkman stressed the idea that growth of blood vessels is related to the growth of cancer. At that time, gifted young physicians could fulfill their obligation to military service by being assigned to conduct scientific research in a prestigious government institution. Folkman was assigned to the Navy hospital in Bethesda, Maryland. The Navy was interested in a blood substitute that could be used for prolonged extracorporeal perfusion and eventual clinical application. At that time, after having worked at the Rockefeller Institute with Charles Lindbergh and Alexis Carrel on the culture of whole organs, I published the outlandish idea of using the oxygen carrying blue pigment of the horseshoe crab, hemocyanin, as a hemoglobin substitute. The Navy had the more sensible idea to use crystalline hemoglobin. Folkman designed a perfusion system, based on Carrel and Lindbergh’s organ culture, to implant tumors into isolated perfused organs. The results showed that implanted tumors grew as solid spheres, but that growth ceased when the transplant reached a size of about 2 millimeters. These tumors did not become vascularized. However, when implanted into the anterior chamber of the eye in the proximity of blood vessels, the tumors grew, showing that vascularization and tumor growth are related. Based on experimental observation, Folkman concluded that the capillary endothelium stimulates cell division and that “the inhibition of angiogenesis may provide a form of cancer therapy worthy of serious considerations.” From then on, the search for the material which promotes angiogenesis of solid tumors became a primary goal. In 1968, I met Dr. Philippe Shubik from Chicago who, together with Melvin Greenblatt, showed in the hamster cheek pouch that a humoral, filterable substance confers angiogenic properties. This insight led to the discovery and identification of a vascular endothelium growth factor by Ferrara and his coworkers. He discovered the active material, vascular endothelial growth factor (VEGF), an endothelial specific mitogen and an angiogenesis inducer in vivo. Several other workers had already anticipated this finding. Ide and associates found in 1939 that tumors elaborate a vessel growth stimulating substance and Algire wrote in 1945 that the growth of tumors “is dependent on the development of a rich vascular supply.” Ferrara later cloned VEGF and found that it is conditioned by follicular pituitary cells. Others showed that hypoxia induces VEGF expression. Of special interest was the finding that tyrosine kinases are VEGF receptors. Inhibition of these enzymes has played a dominant role in the treatment of tumors, as these enzymes represent a novel target for the inhibition of VEGF signaling. The proof of the role of VEGF in tumor angiogenesis required the demonstration that its inhibition prevents tumor growth. The capstone was the finding that neutralizing monoclonal antibodies reduce the growth of VEGF rich glioblastoma cell lines. The previous discovery of hybridoma technology for the production of monoclonal antibodies by two scientists of completely different background made this possible: Cesar Millstein from Argentina and Cambridge and Georges Köhler from Germany, who met at a lecture in Basel, Switzerland. It was a chance meeting which changed the treatment of disease and brought closer the dream of Paul Ehrlich of a magic bullet, a therapy which targets a specific cause of disease.

Judah Folkman died a few months ago while on the way to a meeting. He possessed unbounded enthusiasm and skill of observation. Folkman was born in 1933 in Cleveland, Ohio. He attended Ohio State University and was accepted into Harvard Medical School at the age of 19. During his surgical residency at Massachusetts General Hospital in 1960, he was drafted into the Navy and had the good fortune to be stationed at the National Naval Medical Center in Bethesda. There, inspired by the work of Carrel and Lindbergh, he began his work on tumor angiogenesis in isolated perfused organs. Back in Boston, he (continued on page 6)
Dear Colleagues,

I suppose that, at the time of this writing, many of you are just getting back to work after the summer vacation, and I wish you a productive and rewarding academic year. I suspect you have piles of papers to read; therefore, to make up for the stress that I inflicted upon you with a rather lengthy article in the last issue of HN&V, I have decided to make this column a little shorter than usual.

Following up on the theme of unity that I discussed in my previous article, I wish to address the topic of an annual ISHR dinner. It is one of my goals as President to see to it that the members of the various Sections of the ISHR have a chance to get together as a group at least once a year. I am of the opinion that gathering once every three years (during World Congresses) is not sufficient to promote a feeling of cohesion and unity within the Society. This is the reason why, as Secretary General, I inaugurated the tradition of organizing an annual dinner of the ISHR, which was held in conjunction with the Editorial Board dinner of the JMCC on Monday night during the Annual Sessions of the American Heart Association. My intention to promote an annual ISHR dinner was reiterated in my acceptance speech last year in Bologna.

Why do we need an annual ISHR dinner? As I pointed out in my previous column, unifying the seven Sections of the ISHR is one of the major challenges that face the Society. The adage “far from the eyes, far from the heart” is one of the truisms of life. When members of different Sections do not come together even once a year, it becomes difficult for them to feel that they are part of one Society. Besides, being together with other members from different Sections promotes the idea that our Society is viable, active, and vibrant. The dinner is also a unique opportunity for the ISHR members to meet with the leadership of the Society and be apprised of recent developments, initiatives, and issues of general interest. Virtually every major scientific society holds annual dinners. It is true that ISHR Sections have annual meetings during which members interact with each other. That is obviously important and salutary; nevertheless, it does not, in my mind, replace the need for a meeting among Sections.

While there seems to be a quasi-universal consensus that an annual ISHR dinner would be, in principle, a sensible and rationale idea, a number of pesky operational problems hinder the implementation of this initiative. Here is a quick list.

- **Where?** Practically speaking, the most opportune venue seems to be the annual AHA Sessions in November, because this meeting is likely to have a higher attendance by ISHR members than other meetings.

- **When?** Of all of the days one could choose during the AHA Sessions, Monday seems to be the most suitable, because that is when ISHR members are most likely to be available (many of them do not arrive at the meeting site in time for a Saturday night meeting, many of them attend Editorial Board dinners on Sunday night, and many of them attend Council dinners on Tuesday night).

- **How?** Should the ISHR dinner be a stand-alone event or should it be combined with the Editorial Board dinner of the JMCC (as has been done in the past)? The advantages of the latter solution are that i) total attendance is boosted, ii) ISHR members learn about their journal, and iii) JMCC Editorial Board members are able to attend both events (it is doubtful that they would attend two separate dinners). This
completed his pediatric surgery residency at Massachusetts General Hospital, then moved to the Children’s Hospital where he was appointed surgeon-in-chief at the age of 34. He stepped down in 1981 to devote his full effort to research.

We owe Dr Folkman and Dr Ferrara and all the other pioneers a huge debt of gratitude for opening a new field leading to a promising therapy of cancer. More than fifty angiogenesis inhibitors are today in clinical trial. It is regrettable that Dr Folkman did not receive the highest award that science can offer; he would have richly deserved it. Those of us working in different fields of medical science can only admire his ability to observe experimental phenomena and learn from them. As quoted by Bruce Chabner and his friends, Folkman left us this wonderful wisdom as he wrote: “The problem of understanding the phenomenon of angiogenesis, of working out its biology, of connecting it to a large family of clinical diseases once thought to be totally separate entities, seems to have been tackled in somewhat the same way that the author E.L. Doctorow describes what it is like to write a novel. ‘Writing is like driving at night. You cannot see beyond the headlights, but you can make the whole trip that way’.”

**References**

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The author is most grateful for the generous help of Dr Eugene Braunwald in completing this article.
2007 ISHR Award Winners: Bologna, Italy

David J. Hearse, Ph.D., D.Sc.: Peter Harris Distinguished Scientist Award
“Ischemia, reperfusion and cardioprotection: successes and failures in the journey from laboratory to man”

Prof. Hearse is Professor of Cardiovascular Biochemistry at King’s College London and Co-Editor-in-Chief of Dialogues in Cardiovascular Medicine. Dr Hearse is a pioneer in the field of cardioprotection, and is well-known for his studies on reperfusion injury where he coined the phrase ‘oxygen paradox’. His more recent work in the fields of cardiac surgery and transplantation led to the development and introduction into worldwide use of the St. Thomas’ Hospital Cardioplegic Solution.

Joanne S. Ingwall, Ph.D.: Janice Pfeffer Distinguished Lecture

Dr Ingwall is currently Professor and Co-Vice Chair for Faculty Development in the Department of Medicine at Brigham and Women’s Hospital in Boston, MA. Her current major research interest is cardiac energetics using hearts of transgenic mice designed to mimic specific molecular defects known to occur in ischemia and heart failure. She is a pioneer in the use of magnetic resonance spectroscopy to study cardiac energetics and function.

Eduardo Marbán, M.D., Ph.D. Keith Reimer Distinguished Lecture
“Stem Cells for Cardiac Regeneration”

Dr Marbán is Michel Morowski, M.D. Professor and Chief of Cardiology at Johns Hopkins in Baltimore, MD. He also directs an NIH-sponsored translational research program in stem cells, the Specialized Center for Cell based Therapy. Dr Marbán’s professional career is dedicated to understanding disorders of cardiac rhythm and pump function, and to developing novel treatments based upon fundamental insights into mechanism.

Friederike Cuello, Ph.D.: Richard J. Bing Young Investigator Award
“Regulation of troponin I phosphorylation and myofilament Ca²⁺ sensitivity by protein kinase D in intact ventricular myocytes”

Dr Cuello is an RCUK Fellow in the laboratory of Prof. Metin Avkiran in the Cardiovascular Division at King’s College London. Her major interest is cellular signaling, particularly the regulation and function of protein kinase cascades in myocardial physiology and pathophysiology.
REPORT ON THE XXXII MEETING OF THE AUSTRALASIAN SECTION
(AUGUST 7-10, 2008; ADELAIDE, AUSTRALIA)

The 32nd Annual Scientific Meeting of the Australasian Section of ISHR (ISHR AUS-Section) was held at the Adelaide Convention Centre, Adelaide, South Australia. Adelaide is known as the wine and festival capital of Australia; it is a beautiful city surrounded by parklands, with charming historical buildings, museums, galleries, cafes, pubs and restaurants. For those of us visiting Adelaide for the first time, it was a pleasant surprise to see the surrounding countryside a beautiful green as we flew in. Since 2005, ISHR AUS-Section meetings have successfully run conjointly with the Annual Scientific Meeting of the Cardiac Society of Australia & New Zealand (CSANZ). This partnership has proven fruitful over the years and 2008 was no exception, producing an impressive fully integrated basic science and clinical program focussing on cardiovascular disease diagnosis, treatment and prevention – a program which was sure to have pleased the (just on) 2000 registrants.

This year the prestigious RT Hall Lecturer was Dr Joseph Loscalzo (Boston, USA) who gave an elegant presentation on the “Complexity in Biological Systems and its Implications for Cardiovascular Medicine”, finishing with an 1850 quote from Ralph Waldo Emerson “It is the last lesson of modern science that the highest simplicity of structure is produced not by a few elements, but by the highest complexity.” Prof Robert Graham (Sydney, Australia) delivered the Basic Science Lecture on “The Regenerative Capacity of the Human Heart: Clinical & Therapeutic Implications”, with a wonderful overview of this exciting area showing evidence of some regenerative capacity in the mammalian heart (either by mobilisation of resident cardiac or extra-cardiac stem cells), and the capacity under certain circumstances to induce proliferation even in mature cardiomyocytes.

The Australasian section of ISHR has always encouraged students to present their work at the annual scientific meetings. This is supported by offering a financial contribution towards their travel costs, and by the award of prizes for both oral and poster presentations. This year our student members once again made a major and vibrant contribution to the annual meeting. Student presentations in both the oral and poster sessions were of an extremely high standard. The three finalists for the student Young Investigator Prize all gave outstanding oral presentations, providing the judges with a real challenge in selecting the winner. Ms Christine Ball (The Queen Elizabeth Hospital, Adelaide, Australia) with the title of her talk, “The Role of L- and T- Channels in the Large and Microvasculature.” It must be said that the other finalists, Ms Lavinia Tran (Monash University, Melbourne, Australia) and Ms Lien Lam (Centenary Institute, Sydney, Australia) were also a great credit to the Society.

If anything, the judges for the student poster prize faced an even more difficult task with a number of outstanding student posters being presented at the meeting. Initially it was planned to award only a single poster prize, but because of the high quality of the student posters, runner-up awards were also made. The Best Student Poster prize went to Ms Kate Owen (Baker IDI Heart and Diabetes Institute, Melbourne, Australia) who presented, “The Protective Effects of Exercise and Phosphoinositide 3-Kinase (p110alpha) Activation in a Setting of Heart Failure.” Poster runner-up awards went to Mr Jonathan Mynard (Murdoch Children’s Research Institute, Melbourne, Australia) and Mr Dennis Wolf (Baker IDI Heart and Diabetes Institute, Melbourne, Australia). Congratulations to these students and all the other presenters.

The students also organised a very successful lunch-time ‘Career Development’ workshop that focussed on approaches to seeking post-doctoral positions and early career advancement, with insightful presentations from Prof Ajay Shah and A/Prof Igor Wendt. Many thanks to our ISHR Council student representatives, Ms Christine Ball and Ms Kim Mellor, for organising this event.

A lot of work behind the scenes led
to the success of this meeting. We would like to thank all of the Scientific Committee members - their tireless efforts (including lots of 7:30 am Monday morning meetings in Adelaide!) resulted in an engaging Program. The Committee Chair was Dr John Beltrame and the ISHR representatives were A/Prof Lea Delbridge (ISHR AUS-Section President) and Dr David Saint (Secretary). Dr Sal Pepe (immediate past President) was also very much involved. Prof Tak Wong (Hong Kong) announced his retirement from our Section Council – he has been a great supporter of the meetings and student mentor over the years, and his contributions will be missed. Through the efforts of Dr Julie McMullen (Treasurer) our paid membership numbers increased in 2008, and we hope this trend will continue in the years ahead.

A big “thank you” to A/Prof Igor Wendt, who organized the judging of student talks and posters, and the presentation of student prizes. Last, but not least, thanks to Dr David Saint who organised a superb annual dinner (which incorporated the Annual General Meeting), at a quaint pub-restaurant, bringing members together in a relaxed atmosphere, to enjoy South Australian wine, good food and great discussion.

Helen Kiriazis
Marie Ward
Igor Wendt

You are invited to join us at the 2009 ISHR AUS-Section Meeting
August 13-16, 2009
Sydney Convention and Exhibition Centre, Sydney, Australia

This will be a joint meeting with the Cardiac Society of Australia and New Zealand and will combine cutting edge science with the latest clinical developments in cardiovascular disease.

Details can be found at: www.csanz.edu.au
The Incessant Remodelling of Mitochondrial Studies in Cardiovascular Research

by Fabio di Lisa, M.D., F.I.S.H.R.

The following lines are meant to summarize how mitochondrial research contributed to changing the approach to cardiovascular research from the description of phenomena into the elucidation of causal relationships and pathophysiological mechanisms. It does not cover all the efforts made in investigating cardiac mitochondria. In fact, and unfortunately, many relevant contributions are not mentioned due to space constraints.

Due to the abundance of mitochondria in cardiac myocytes and to the strict dependence of myocardial function on oxidative phosphorylation, it is hardly surprising that studies focused on these organelles go hand in hand with the development of cardiovascular research in the direction of molecular and cellular cardiology. In fact, the understanding of metabolic pathways and ATP synthesis, as well as ATP utilization for contraction and ion homeostasis, allowed the integration of the physiological analysis of flow and pressure with the biochemical investigation of intracellular events. This holds especially true for research related to myocardial ischemia and cardio–protective interventions starting during the 1960s, soon after it became clear that mitochondria are the site of oxidative metabolism and energy conservation. Pioneers in the study of myocardial metabolism, such as Richard J. Bing and Lionel H. Opie, were also the founding fathers of both the Journal of Molecular and Cellular Cardiology and this Society, the infancy and early developments of which were precisely chronicled by Dr Opie in Heart News and Views.

Concomitantly, due to the seminal contribution of Robert Jennings, it became clear that ischemia, and especially post–ischemic reperfusion, are associated with profound mitochondrial derangements related to intracellular Ca²⁺ overload.

In those years, I was totally ignoring mitochondria and stumbling on Latin and Greek; yet I remember four musicians singing “I’m fixing a hole where the rain gets in and stops my mind from wandering where it will go”. Maybe this was the first description of the permeability transition pore (PTP) and the protection afforded by its inhibition. Fortunately, the Fab Four stopped wandering, so that many years later, a few of us were left with the opportunity to relate PTP opening to myocardial ischemia. Anyway, it is an amazing coincidence that the birth (or the Big Bang) of molecular and cellular cardiology occurred concomitantly with many social changes and the explosion of pop music. I see it as a time in history blessed by creativity and passion.

During the 1970s, cyanide was found to decrease reoxygenation injury. This seminal observation was preceded by the description of the so-called “Ca²⁺ paradox” and followed by other paradoxical observations that can be attributed to mitochondrial alterations. More importantly, the notion was introduced that mitochondria are not only important for the maintenance of myocardial function and viability, but also for determining cell death. This concept was later extended by the understanding of the crucial role of mitochondria in apoptosis. Another relevant paradox, again discovered in Jennings’ laboratory, was the so-called “ischemic preconditioning”. This phenomenon is now also attributed to mitochondria, and cardio–protection, in particular, is likely to depend on a decreased susceptibility to PTP opening.

The interest in myocardial metabolism was heightened during the 1970s and 1980s by the identification of crucial steps of oxidative metabolism that are altered during ischemia and reperfusion. The notion that myocardial protection is afforded by favouring glucose oxidation while limiting fatty acid consumption was defined in that period, and this discovery continues to prompt important studies that are now focused on signaling pathways and control of mitochondrial biogenesis.

By the end of the 1980s, mitochondrial research seemed to be ready for retirement. The mechanisms ruling respiration and ATP synthesis were defined and the concept of metabolic protection of the heart was well–established. Yet, it must be pointed out that, based on current standards, the initial discoveries of the contribution of mitochondria to cardiac pathophysiology would be rejected by any reviewer as mere phenomenological associations. Indeed, novel tools were...
needed to change descriptive studies into conclusive demonstrations of mechanisms operating in vivo. The exponential growth of cell and molecular biology revitalized the entire field by providing insights into underlying mechanisms and causal relationships. In particular, between the end of the 1980s and the beginning of the 1990s, advancements in fluorescence microscopy along with the introduction of a wide array of fluorescent probes allowed researchers to monitor changes of mitochondrial Ca\(^{2+}\) and membrane potential in intact cells. A peculiar technique based on calcein fluorescence was developed in our laboratories for investigating the occurrence of PTP opening. All of these techniques were exploited to elucidate the role of mitochondrial dysfunction in apoptosis and are now available for defining the contribution of mitochondria to autophagy. Fluorescence microscopy has also been a major tool for defining the occurrence and the relevance of mitochondrial generation of reactive oxygen species.

In the last decade, the impact of cell biology has been extended and strengthened by advanced techniques of protein analysis. The deletion of mitochondrial proteins, such as SOD, adenine nucleotide translocase, cyclophilin D and p66Shc, and the genetic impairment of mitochondrial DNA repair have not only provided phenomenal demonstrations of the tight links between mitochondria and cardiovascular diseases, but have also indicated relevant targets for novel and focused therapeutic approaches, as was recently validated in patients undergoing myocardial ischemia.

Despite these exciting discoveries, a large number of unsolved issues keep mitochondrial research relentless. The molecular identity of mitochondrial cation transporters, including ATP-dependent K\(^+\) channels and the permeability transition pore, are far from being elucidated, leaving room for pharmacological approaches performed with non-specific compounds. It is not yet clear how processes occurring in the outer mitochondrial membrane are connected with alterations of energy-linked activities of the inner mitochondrial membrane. This lack of information also applies to the modulation of processes located in the inner mitochondrial membrane or in the matrix space by signalling pathways originating in the sarcosome or in the cristae. Matters are further confounded by arguable attempts to explain in vivo processes with results obtained in purified proteins or isolated mitochondria.

In a well known letter to his son, Einstein wrote “life is like riding a bicycle. To keep your balance, you must keep moving.” Undoubtedly, this is, and will remain the case for studies related to heart mitochondria, as well as for the ISHR.

References

It was a great honour to receive the 2008 Young Investigator Award at the XXVIII annual meeting of the European Section in Athens, Greece, for my work on nuclear protein import and oxidized low-density lipoprotein (oxLDL). Originally from Lebanon (Douma), I came to Canada to study at “Université de Sherbrooke”, Quebec, where I completed my PhD in the Department of Anatomy and Cell Biology in 2006 with Dr Ghassan Bkaily. Because of my introduction to nuclear membrane function in hereditary cardiomyopathy during my PhD studies, and because this entire area is critical for cell function and viability, I decided to move to the St Boniface General Hospital Research Centre in Winnipeg, Manitoba, Canada and undertake my postdoctoral training with Dr Grant N. Pierce. He is, to my knowledge, one of a very few scientists studying the role of nuclear transport in pathologies of the cardiovascular system. Therefore, my project focuses on the understanding of nuclear import during vascular pathologies such as atherosclerosis. In the present study, we suggest that one of the mechanisms whereby oxLDL alters vascular smooth muscle cell (VSMC) proliferation and apoptosis is through an action on nuclear protein import.

Nuclear Protein Import Plays a Central Role during Cell Proliferation and Cell Apoptosis

Nuclear transport is defined as the movement of molecules in and out of the nucleus through a specific channel called the nuclear pore complex (NPC). Some molecules, such as mRNA, are exported from the nucleus to initiate protein expression. Others, such as transcription factors, signalling proteins, and DNA binding proteins, are imported into the nucleus to regulate gene expression through a process called nuclear protein import (NPI). This highly regulated process is known to accompany specific cell stages (differentiation, transformation, and proliferation).

It is somewhat surprising that our knowledge is still very limited about one of the largest and most vital channels in the cell, the NPC, during pathologies that present an alteration in cell growth as a major part of the disease, such as atherosclerosis. Atherosclerosis is the most frequent cause of death today, and yet we have had limited success in developing approaches to treat this disease. It has been demonstrated that oxLDL is implicated in atherogenesis by inducing not only VSMC proliferation but also VSMC apoptosis. Because cell growth is regulated by protein transport into the nucleus, we hypothesized that the mechanism whereby oxLDL affects proliferation or apoptosis is through an action on NPI.

OxLDL-treated VSMCs Show an Alteration in Cell Growth Associated with an Alteration in NPI through MAPK Activation

Our data showed that a short exposure of VSMC to oxLDL, but not native LDL, induced cell proliferation and favoured cell cycle progression by increasing the
expression levels of proliferation markers such as PCNA. Conversely, longer exposure times to oxLDL decreased VSMC proliferation and the expression levels of PCNA, but increased the expression of apoptosis markers such as PARP (Fig. 1).

In order to determine the intracellular mechanisms responsible for changes in cell proliferation as well as the expression of proliferation and apoptosis markers following oxLDL exposure, we monitored NPI in VSMC using the microinjection technique. This technique consists of injecting cells with an import substrate to visually monitor the transport of the protein from the cytoplasm to the nucleus of a cell. It has taken a great deal of time and work, but we are very proud that we have now perfected an extremely useful and valuable technique to monitor NPI. The import substrate is composed of bovine serum albumin coupled to a BODIPY-FL fluorophore attached to a peptide constructed to contain the SV 40 Large T antigen NLS (CGGGPKK–KRKVED) (Ref. 1) (Fig. 2). NPI is a critical regulatory step in gene expression. In our previous studies, we found that inhibiting the translocation of cell cycle proteins from the cytoplasm to the nucleus was associated with diminution in cell growth by oxLDL (Ref. 2). Therefore, we concluded that oxLDL may directly alter the rate of NPI in VSMC. In our current study, shorter exposure times to oxLDL, but not to native LDL, resulted in an increased rate of NPI whereas longer exposure inhibited NPI (Fig. 3 A-F).

Figure 2. Nuclear protein import in microinjected VSMCs. Panels A-E represent confocal images of VSMC microinjected with Alexa 488-BSA-NLS substrate contained in a micropipette into a single cell. Images were taken before (A) and after injecting (B-E) cells followed by set time points to observe the rate (F) of nuclear import (represented as a ratio nucleus/cytoplasm) for each cell over time. The signal strength in the nucleus is proportional to the amount of substrate present in the nucleus. The pseudocolor scale represents the intensity of fluorescence levels from 0 (black color) to 255 nm (white color). Values are means ± SEM.

Figure 3. Exposure of VSMC to oxLDL induces an alteration in NPI through a MAPK-dependent mechanism. Rabbits aortic VSMC were exposed for different times (3h to 48h) and different concentrations (10, 25 and 50 µg/ml) to oxidized LDL (oxLDL) (E to J), native LDL (naLDL) (C and D), or control (A and B). Representative confocal images of microinjected cells with Alexa 488-BSA-NLS substrate following a short (6h) or a longer (48h) exposure to 25 µg/ml oxLDL, naLDL or Control. These figures show the NPI in VSMC at 30 min post-injection. The pseudocolor scale represents the intensity of fluorescence levels from 0 (black color) to 255 nm (white color). PD: PD98059; SB: SB203580.

One potential mechanism that could explain the changes in the rate of NPI by oxLDL is the alteration in the number of nuclear pores (p62) that span the nuclear envelope. Indeed, short exposure of VSMC to oxLDL did induce a significant

(continued on page 14)
expression caused a significant decrease in pore expression. Conversely, (continued from page 13)

increase in pore expression. Conversely, longer exposure times of VSMC to oxLDL caused a significant decrease in pore expression (Fig. 1).

In order to better understand the changes in NPI, NPC expression, and cell growth following oxLDL exposure, we hypothesized that the MAPK pathway may be implicated. This intracellular signalling pathway has been involved in the development of atherosclerosis. We decided, therefore, to study the effect of MAPK inhibitors (SB203580 and PD98059) on VSMC exposed to oxLDL. The increase in NPI in VSMC following a short exposure to oxLDL was an ERK MAPK-dependent mechanism (Fig. 3 G-H). However, the decrease in NPI in VSMC following a longer exposure to oxLDL was a p38 MAPK-dependent mechanism (Fig. 3 I-J). The activation of the pp38 MAPK by oxLDL correlates with previous findings showing that ceramide, a pro-apoptotic agent, decreases NPI by stimulating the p38 MAPK pathway (Ref. 3).

Conclusions and Future Directions
This study identifies NPI as the missing link between oxLDL and cell growth during atherosclerosis. Thus, NPI represents a potential target for developing drugs to treat hypertrophy, angiogenesis and a variety of diseases such as hypertension, cancer, viral infection (HIV), and diabetes.

References

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David Eisner has been at The University of Manchester since 1999 and has held the British Heart Foundation Chair of Cardiac Physiology since 2000. His undergraduate degree was obtained at the University of Cambridge and he did graduate work at Oxford with Denis Noble, graduating in 1979. He was on the Faculty at University College London (1980-90) and the University of Liverpool (1990-1999) before moving to Manchester.

Dr Eisner has been awarded a Wellcome Trust Senior Lectureship, The Pfizer Award in Biology and The Wellcome Trust Physiology Prize. He has served as Chairman of the Editorial Board of The Journal of Physiology and is a member of the Editorial Boards of The Biophysical Journal and Circulation Research. Since January 2008 he has been Editor in Chief of The Journal of Molecular and Cellular Cardiology. He is a member of the International Council of the ISHR, having previously been on the Council of the European Section. In 2006 he co-organized the Annual meeting of the European Section in Manchester. He is a Fellow of the ISHR and of the Academy of Medical Sciences.

Dr Eisner’s research has focused on the basic mechanisms regulating intracellular sodium and calcium concentrations. He demonstrated the steep dependence of contraction on intracellular sodium concentration and thence the role of sodium calcium exchange (NCX) in mediating interactions between Na and Ca regulation. After developing a method to measure the Ca content of the sarcoplasmic reticulum (SR), he characterized the mechanisms responsible for the normal, stable control of SR Ca content. His work demonstrated that SR Ca content is controlled by the systolic Ca transient modulating fluxes of calcium across the sarcolemma. This mechanism explains many, previously perplexing, aspects of calcium regulation including the fact that changes in the properties of the SR Ca release channel (Ryanodine Receptor) have no effect in the steady state on the amplitude of the calcium transient due to changes of SR Ca content. Perturbations in this regulation may be responsible for disorders such as pulsus alternans. His recent research has focused on the mechanisms responsible for the generation of the diastolic Ca waves that are known to be responsible for some cardiac arrhythmias and how therapeutic strategies might be developed to abolish these arrhythmias.

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**The Keith Reimer Distinguished Lecture 2008**

**Honored Speaker: David Eisner, D.Phil.**

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