Countdown for World Congress XX has started

The countdown for the World Congress has started. We have only two months before the big event for our Society. I am greatly honored to inform you that over seven hundred abstracts were submitted, and we have accepted 706 presentations for moderated poster sessions. All of the abstracts report a high quality of research; there is no doubt that the meeting in Kyoto will be successful and exciting. As I noted in the previous issue of this newsletter, the Scientific Program comprises 50 symposia; including 11 Section-sponsored symposia, all of which are excellently composed to cover the wide scope of cardiovascular research interests. I would like to thank all of the members of the scientific program committees (SPCs) (the ISHR SPC, the Congress SPC, the International Advisory Committee, the Local Advisory Committee and the Section Executive Committee) for their dedicated efforts to make the program so exciting. Indeed, the programs of the symposia integrate presentations addressing topics ranging from gene to life and diseases under the main theme of “Paradigm Shift to Integrated Cardiology – Gene, function and life”.

Meeting participants can also enjoy many Award lectures, a Nobel laureate lecture and an invited special lecture as highlights of the scientific program. Furthermore, the early career researcher (ECR) workshop and morning sessions for young researchers are set up to provide many learning opportunities. We also look forward to the active participation of early career investigators in the Richard Bing YIA Award and Poster Awards. In the evening, meeting participants will enjoy a get-together, a delicious Banquet, and satellite sessions focusing on new cardiovascular drugs.

Kyoto holds a very special place in Japanese culture; it was the old capital for more than 1000 years, and thus offers a vast choice of activities for visitors involving the arts, entertainment, cuisine and fashion. You can enjoy a visit to many famous temples and shrines, and I arranged a special outing for you to enjoy the Aoi-Festival on May 15th as a half-day excursion. Don’t miss this big event, the most solemn and graceful festival in our country. I promise a memorable and rewarding experience to all attendees. Please register now if you have not yet done so. For Congress information, visit our website at www.ishr2010.com. I look forward to seeing you in Kyoto soon.

Masatsugu Hori, MD, PhD
President, XX World Congress of ISHR
CONGRESS SCHEDULE/SCIENTIFIC PROGRAM

[Thursday, May 13]

[Friday, May 14]
Invitation to XX World Congress ISHR
May 13–16, 2010 in Kyoto, Japan

You are cordially invited to join us in Kyoto. We promise a memorable and rewarding experience to all attendees.

200 outstanding speakers are invited for 50 symposia on cardiovascular science under the theme “Paradigm Shift to Integrated Cardiology-Gene, Function and Life”
Over 700 abstracts submitted for free communications!
Nobel Laureate lecture, special lecture and ISHR Award lectures as the highlights of the Congress

Register now! Early bird registration is until March 31, 2010.

Nobel Laureate Lecture
NLL. Oliver Smithies (University of North Carolina at Chapel Hill, USA)
“Turning pages: from gels to genes”

Special Lecture
SL. Shinya Yamanaka (Kyoto University, Japan)
“Induction of pluripotency by defined factors”

Award Lectures
Distinguished Lecture Awards:
Keith Reimer Distinguished Lecture Award (KRDLA)
“Phenotypic responses due to induced genetic ablation of cMyBP-C in adult mice”
Richard L. Moss (University of Wisconsin, USA)
Janice Pfeffer Distinguished Lecture Award (JPDLA)
“Regulation of myocardial growth and death by oxidative stress”
Junichi Sadoshima (University of Medicine and Dentistry of New Jersey, USA)
President’s Distinguished Lecture Award (PDLA)
“A novel molecular mechanism and regeneration therapy for heart failure”
Issei Komuro (Chiba University/Osaka University, Japan)

Outstanding Investigator Award (OIA)
“Thrombospondin4 is a novel regulator of ER stress adaptation and cardioprotection”
Jeffery D. Molkentin (Cincinnati Children’s Hospital Medical Center, USA)

Research Achievement Award (RAA)
“20 years of changing the heart: to the sarcomere and beyond”
Jeffrey Robbins (Cincinnati Children's Hospital Medical Center, USA)

Peter Harris Distinguished Scientist Award (PHDSA)
“Protecting the ischemic heart”
James M. Downey (University of South Alabama, USA)

Symposia
S1. Thrombus and anti-platelet treatment for ischemic heart disease
S2. Cardio-renal interaction in heart failure
S3. Genetic background of lethal arrhythmia
S4. Mitochondria in cell life and death
S5. Calcium signaling in cardiac dysfunction, cell death and remodelling
S6. MicroRNAs in cardiovascular development and disease
S7. Signaling survival
S8. Myocardial stress: ROS, ischemia and inotropy
S9. Pathophysiology and treatment of diastolic heart failure
S10. Pathophysiology of pulmonary hypertension and right heart failure
S11. Lipid metabolism and atherosclerosis
S12. Mitochondria in myocardial ischemia and reperfusion
S13. Sodium homeostasis and cardiac function
S14. Genetic mechanisms of myocardial disease
S15. Mechanisms of cardiac electrical and mechanical dysfunction and repair
S16. Calcium handling and signaling proteins: regulation and dysregulation
S17. Vulnerable plaque and aborted rupture (including; RAS)
S18. Genetic background in aging
S19. The race for the implantable cardiomyocyte: who is winning?
S20. Cardioprotective interventions in acute ischemia
S21. Toll-like receptors, heat shock, inflammation and the heart
S22. Sarcomeric signals in health and cardiac disease
S23. Influence of major cardiovascular risk factors on cardioprotective mechanisms
S24. New strategies for stem cell therapy and vascular generation
S25. RAAS activation and remodeling of the failing heart
S26. Vascular endothelial function and cardiovascular events
S27. Stem cell fate determination
   (Kaito Symposium in Memory of Yoshio Ito (ISHR President 1989-92))
S28. Emerging therapeutic approaches in ischemic heart disease
S29. Novel protein signaling mechanisms in the heart
S30. Modulation of myocardial contraction by modification of sarcomeric proteins
S31. Animal models of hypertrophy and failure: what have we learned?
S32. Diabetes and atherosclerosis
S33. Mechanistic insight for better management of hypertension
S34. Use of stem cells to repair infarcted myocardium
S35. Novel effectors and modulators in cardiac hypertrophy and failure
   (Bayer Yakuhin Symposium in Memory of Howard E. Morgan (ISHR President 1983-86))
S36. Nitric oxide signaling in the cardiovascular system
S37. Eicosanoids and vascular function
S38. Novel approaches for treatment of heart failure
S39. Novel insights in adipocytokins and cardiovascular disease
S40. Tissue engineering for the heart
S41. Protein processing and quality control
S42. p38 MAPK inhibition in myocardial infarction and remodelling: beside the bedside?
S43. Protection from cardiovascular injury
S44. Mechano-transduction and vascular biology
S45. Novel anticoagulant treatment for atrial fibrillation
S46. Molecular mechanisms of myocarditis and heart failure
S47. Vascular injury, repair and regeneration
   (Canon Symposium in Memory of Normal R. Alpert (JMCC Editor 1993-98))
S48. Mechanisms of redox signaling
S49. Cancer versus heart disease: can we cure both?

Tutorial Sessions
TS1. How to apply imaging techniques to explore cardiovascular signaling
TS2. JMCC Early Career Workshop “Publishing and its Perils”
TS3. Career Development Workshop
TS4. How to apply mass spectrometry to heart research

Free Communications (Moderated Poster Sessions)

Luncheon Seminars (Industry-sponsored 14 sessions)

Satellite Seminars
SS1. New drugs and diagnostic biomarkers for cardiovascular diseases
SS2. Promising future drugs for cardiovascular diseases

ISHR Section Meetings
REGISTRATION

- All participants are requested to register for the Congress.
- Advance registration at a special rate is available until Wednesday, March 31, 2010.

**Registration fee (per person):**

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<th>Category</th>
<th>Until Wednesday, March 31, 2010</th>
<th>After Thursday, April 1 till Sunday, May 3, 2010/On-site</th>
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<tr>
<td>ISHR members</td>
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<td>Students*</td>
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<td>Accompanying persons</td>
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* Student registration: To qualify for these rates, the registrant must be (a) a member of the ISHR (membership applications may be submitted through Section secretaries or online - see the ISHR web pages at www.ishrworld.org), (b) enrolled in an official training program (e.g. PhD studentship) at his/her institutions at the time of the Congress. Written certification or copy of student ID confirming must be provided by the registrant’s Head of Department or equivalent.

**Registration includes:**

1) Admission to the get-together reception (May 13), banquet (May 15), all scientific programs and the Commercial Exhibition
2) A book of abstracts and a program booklet
3) Admission to all morning tutorial seminars, luncheon seminars and satellite seminars
4) Aoi Festival half-day excursion (May 15)

**How to register:**

- Registration for the Congress should proceed only ONLINE. By completing the registration, hotel & tour reservations can be made.

**Deadline of advance registration:** **Wednesday, March 31, 2010**

*After Thursday, April 1 till Sunday, May 3, 2010, registration can be made at the on-site registration rate.

Note: Those whose abstracts are accepted are requested to register for the Congress with the remittance of the registration fee before Wednesday, March 31, 2010. Otherwise, the abstracts cannot be included in the program.

SOCIAL PROGRAMS

**Get-together reception:**

Date       Thursday, May 13, 18:40
Place      Swan Banquet Hall, Kyoto International Conference Center

**Aoi Festival half-day excursion:**

Date       Saturday, May 15, a.m.

**Banquet:**

Date       Saturday, May 15, 18:20
Place      Swan Banquet Hall & Garden, Kyoto International Conference Center

*Buffet style/Dress informal
The National Institutes of Health (NIH) in Washington, D.C. have grown into a behemoth of science – made up of 27 institutes and centers, and employing over 19,000 people, 6,000 of whom are scientists. One of the main functions of the NIH is the financial support of research in the life sciences, particularly medicine. How did the NIH become the irreplaceable sponsor of the life sciences? How did they develop into supposedly wise organizations which hand out strict punishments or glorious rewards?

It all began in 1670, when American Indians ceded all claims to Staten Island to the English in a deed to Governor Francis Lovelace, six years after English soldiers had conquered New Netherlands. As an irony of history, some Staten Island men signed an oath of allegiance to the British crown in 1776, on the same day that New York received word of the signing of the Declaration of Independence in Philadelphia.

In 1887, one room in the Marine Hospital on Staten Island, New York, was occupied by a laboratory belonging to the Marine Hospital Service. This room was the cradle of the National Institutes of Health. The Marine Hospital Service was established in 1798 to take care of the ills of merchant seamen. One of its main functions was to examine and isolate passengers who had arrived in New York harbor with dreaded diseases such as yellow fever and cholera. The question was how and where to isolate these unfortunate victims. Finally, a series of “pest houses” were built around New York Harbor to isolate these patients. The “pest houses” did not fare well amongst their neighbors. On September 1, 1848 mobs torched the Marine Hospital quarantine where immigrants with infectious disease were held. This quarantine station was soon replaced by others built from landfill on artificial islands.

Staten Island was strategically located to receive the ill, and a number of isolation facilities were built there. It was the time of the ascendancy of microbiology, of Koch, Pasteur, Wassermann, Metchnikoff, Ehrlich and others. Bacteriology was then what molecular biology is now: the wave of the future.

In 1887, the Marine Hospital Service recruited a young bacteriologist, Joseph J. Kinyoun to set up a laboratory in the Marine Hospital. There are several photographs of the room and its equipment, which consisted primarily of one Zeiss Microscope. Kinyoun called this room “Laboratory of Hygiene.” He became its first director followed by a series of men who usually stayed 2 years in office, during which time they had to placate members of Congress, the President of the United States, and the scientific community. Not an easy balancing act!

The year 1891 was pivotal for the healthcare of the United States. In that year the Hygienic Laboratory with Dr. Kinyoun was moved from Staten Island to Washington, D.C. At the beginning of the 20th century, in 1931, the “Hygienic Laboratory” was renamed the National Institutes of Health. These changes sound quite seamless, but in reality they were not easily accomplished. One of the main obstacles for the Washington laboratory was the acquisition of the ground it was to occupy. The location of the new institute was to be in Bethesda, Maryland with its meadows, golf courses and farmhouses. Much of the ground desired by the new institute belonged to Luke Wilson and his wife Helen, who attempted to leave their property to a charitable institution. They were not successful, and finally wrote a letter to President Roosevelt offering their land as a donation to the Federal Government. In 1935, the Wilsons agreed to donate their land to NIH. From then on, the institutes grew into the gigantic organization we know today.

In 1937, looking at different job opportunities, I was told of Staten Island Hospital as an up and coming research facility. I took the very pleasant ferry ride from Manhattan, but at that time the transfer of the Marine Hospital from Staten Island to Washington DC had already taken place. What happened to the sibling of the Marine Hospital, left behind in Staten Island? In contrast to the vigorous Bethesda branch, it limped along with federal help. In 1939, FDR ordered the construction and maintenance of a public health service hospital and the Staten Island Public Health Service Hospital was built. It was eventually sold to the Sisters of Charity who renamed it Baley Seton after New York’s Saint Elizabeth Ann Seton and her father Richard Baley, an American born British army revolutionary war surgeon. In 2000, the Sisters of Charity turned the hospital over to the St. Vincent Catholic Medical Center and, in 2003, the
hospital complex was sold to become the Richmond University Medical Center. But the future of the cradle of the National Institutes of Health has remained uncertain.

What about Dr. Kinyoun? His life was more than a list of statistics. He was a courageous scientist who honestly reported what he found, and bore the consequences. Joseph James Kinyoun was born in 1860 in Centerview, Missouri, the son of a physician. He attended St. Louis Medical College and, like his father, graduated from Bellevue Hospital Medical College in 1882. As he was interested in research he entered the Carnegie Laboratory to complete a course in pathology and bacteriology. He then became an assistant surgeon in the Marine Hospital Service and, as noted above, took over the direction of the one room lab on Staten Island, New York. In 1891 the Surgeon General moved the lab and Kinyoun to Washington, DC. He frequently traveled to Europe to work with leading bacteriologists.

Kinyoun’s fortunes took a bitter turn in 1899 when he was assigned to San Francisco. There he detected Bubonic Plague in Chinatown. When he made his findings public, the Governor of California and various other authorities tried to silence him. When he refused, he was accused of false statements and his career was sacrificed. Dr. David Morens calls him the first U.S. Health Officer accused of bioterrorism. As Kinyoun wrote then, “I am charged…to have deliberately imported plague cultures into California, and inoculated Chinese bodies in order to get up a plague scare and ruin the state.” He was forced to resign from the service. Later he was proven to have been right.

This was a terrible blow for an honest and dedicated man. Kinyoun Houts, his descendent, writes, “After 16 years of what must be considered an exceptional and public career, he now once again became a private doctor. He worked first for private companies but eventually accepted a professorship at George Washington University.” He died in 1919. Thus the first head of the National Institutes of Health had to endure the pitfalls of politics in his public career.

And so as the Institutes grew, their size became both a blessing and a curse. Personal contact between donor and recipient became difficult and the minutiae of bookkeeping became of disproportionate importance. On the other hand, many advances in medicine and science would have been impossible without the Institutes. One can only hope that the spirit of Kinyoun will be kept alive to benefit the sick and suffering. It is for them that the Institutes were built.

References


Harden VA. Short History of the U.S. National Institutes of Health (personal communication, November 12, 2009)

Houts JK. Dr Joseph James Kinyoun Biographical Sketch (personal communication, November 28, 2009).


Morens DM. 2009, Abutment: Joseph James Kinyoun, M.D., Ph.D., presented to the colleagues in the National Institute of Allergy and Infectious Diseases. Bethesda, Maryland

Richard J. Bing, M.D.

FINALE

It is with gratitude and regret that I report that the article on this page is the final installment of Dr Richard J. Bing’s “Past Truth & Present Poetry” history-of-medicine series. This article is the 42nd in the series which began 14 years ago in response to a fortuitous invitation from Dr Tom Ruigrok, Founding Editor, following a concert of chamber music composed by Dr Bing. The first 28 of these articles was published in 2006 as a book entitled, “Past Truth & Present Poetry – Medical discoveries and the people behind them” (ISBN 1903378443). Last year, an omnibus of articles #29-40 was published by the author.

As Dr Bing noted in his first article (HN&V Vol 4:2), “the term ‘past truth’ refers to factual events accompanying a scientific discovery while ‘present poetry’ stresses their human, romantic aspects.” The Editors would like to thank Dr Bing for the knowledge we have gained from his ordered recounting of the historical evolution of the understanding and treatment of cardiovascular disease, and for sharing his personal insights into the human beings involved in the unfolding drama. We are grateful for the generous gift of his time and accumulated wisdom.

Leslie Anderson Lobaugh, Editor, HN&V
William Harvey and the Discovery of the Circulation of the Blood

Part III

Dear Colleagues,

Hereewith please find the third and final part of my account of William Harvey’s life and work.

In the final part of his treatise, De Motu Cordis, Harvey addressed how the blood flows from the right side to the left side of the heart. He was not the first one to describe the pulmonary circulation. At least two people described this before him. One was a Syrian physician, Ibn al-Nafis, who lived in the 13th century and correctly described the circulation of blood from the right ventricle to the lungs and then back to the left ventricle. However, since his writings were never translated into Western languages, these concepts were unknown to the Western world. The second person who described the pulmonary circulation was Michael Servetus, who did it about a century before Harvey. He published these ideas in a religious book, not a scientific book, which is one of the reasons they were unknown at Harvey’s time. The second reason they were unknown was that Servetus was accused of heresy by John Calvin and burned alive in Geneva along with many of his books, and so they were not read. Harvey rediscovered what had already been discovered by these two people. He showed clearly that there are no such things as pores in the ventricular septum (as Galen had asserted), and that blood flows from the right ventricle to the lungs, and then back to the left ventricle.

The only thing that was missing to complete the loop (no pun intended) was the answer to this question: how does the blood go from the arteries to the veins? Harvey struggled with this “gap” but could not fill it, since he did not have the tools to address the question. So, he postulated the existence of pores in tissues, but it was not until 1660 (three years after Harvey’s death) that Marcello Malpighi, using the microscope – which was not available at the time of Harvey – discovered the existence of capillaries in tissues.

In De Motu Cordis, Harvey summarizes his new paradigm thus: “For a long time, I turned over in my mind such questions as, ‘How much blood is transmitted and how short a time does its passage take?’ Not deeming it possible for the digested food mass to furnish such an abundance of blood… unless it somehow got back to the veins from the arteries and returned to the right ventricle of the heart, I began to think whether there might not be a movement, as it were, in a circle. Now this I afterwards found to be true; and I finally saw that the blood, forced by the action of the left ventricle into the arteries, was distributed to the body at large, and its several parts, in the same manner as it is sent through the lungs, impelled by the right ventricle into the pulmonary artery, and that it then passed through the veins and along the vena cava, and so round to the left ventricle in the manner already indicated.”

Naturally, this was a revolution in medicine, for it was a direct contradiction of 1500 years of Galenism. As is the case for any paradigm change, it set off a storm in medical and philosophical circles. Harvey was attacked viciously. For example, the University of Paris opposed his concepts for at least 50 years after it was published. Apparently his medical practice also suffered from the publication of De Motu Cordis. Harvey himself was trepid, because he wrote: “It is of a so novel and unheard-of character, that I not only fear injury to myself from the envy of a few, but I tremble lest I have mankind at large for my enemies, so much does want and custom, that has become as another nature, and doctrine once sown and that has struck deep root and rested from antiquity, influence all men”. Interestingly, he did not hold the media in high regard, lamenting a problem that was a harbinger of much worse things to come. He wrote that “the crowd of foolish scribblers is scarcely less than the swarms of flies in the height of summer, and threatens with their crude and flimsy productions to stifle
us as with smoke.” Things have not changed much, for today almost everything that is reported by the media is grossly distorted, crassly inaccurate, maliciously fabricated, or blatantly false.

What is William Harvey’s legacy? I believe it is twofold. Of course, he discovered the circulation of the blood. This was a turning point for medicine, because it enabled us to understand the human body in a manner that was impossible before. But this is not his major contribution. I think his major contribution has been the establishment of the scientific method in biomedical research. Much has been said about Francis Bacon being the inventor of the scientific method but, actually, Bacon never used it – at least not in biological disciplines. Harvey was the first to use the scientific method in biology. He established experimentation as the principal means for biological research, an approach that we refer to as “inductive reasoning” or “experimental method”, as opposed to believing blindly what Aristotle, Galen, and others had said, or following one’s personal ideas or preconceptions. Harvey must be regarded as one of the founders of modern science because he was the first to adopt the scientific method for the solution of biological problems and to study biology in a quantitative manner. This was an enormous paradigm shift, a paradigm that every scientist has followed since then and that has become the very foundation of modern biology. Harvey was to physiology what Vesalius was to anatomy. Vesalius had debunked Galenic anatomy with his “Fabrica”. Harvey did the same thing in physiology with “De Motu Cordis”. Thanks to these two Galen “bashers”, medicine awoke from a long sleep and shook off the shackles of ignorance and authority. And what a long sleep it was – from the 2nd century until the 17th century A.D.

In De Generatione Animalium, Harvey writes: “Nature herself must be our advisor; the path she chalks must be our walk. For as long as we confer with our own eyes, and make our ascent from lesser things to higher, we shall be at length received into her closet-secrets.” So, we must always rely on our own observations and our own reason, making small but solid steps from “lesser things” to “higher”; if we do so, we will gradually begin to unravel the mysteries of nature.

I want to close this essay by citing some marvelous and eternally inspiring words written by Harvey in the preface to “De Motu Cordis”: “True philosophers [“philosophers”, at Harvey’s time, was a term for “scientists”], who are only eager for truth and knowledge, never regard themselves as already so thoroughly informed, but they welcome further information from whomsoever and from whencesoever it may come; nor are they so narrow-minded as to imagine any of the arts or sciences transmitted to us by the ancients in such a state of forwardness or completeness that nothing is left for the ingenuity and industry of others; very many, on the contrary, maintain that all we know is still infinitely less than all that still remains unknown; nor do philosophers pin their faith to others’ precepts in such wise that they lose their liberty and cease to give credence to the conclusions of their proper senses.” The clause I underlined and italicized is one of the most important statements I have ever seen. Everybody should keep it in mind, particularly those modern scientists who arrogantly think that they know - and can explain - everything or almost everything. This statement reminds me of Socrates, who used to say: “I am wise because I know that I do not know”.

This is Harvey’s immortal legacy, as precious and relevant now as it was 400 years ago. He advises us to be critical, to be skeptical, to challenge what we are taught, to rely on our observations, and to follow our reason. Above all, he tells us that a true scientist knows how limited our understanding of nature is. The experience of scientific inquiry teaches us that the process of answering a question inevitably creates even more questions; this has not changed in the 400 years since Harvey, and will not change in the future. For all the progress we have made, a true scientist has the humility to always keep in mind that “all we know is still infinitely less than all that still remains unknown”.

Roberto Bolli, M.D.
In 2009, the ISHR Australasian Section Annual Scientific Meeting was (as is now usual) held jointly with the Cardiac Society of Australia and New Zealand (CSANZ). The meeting, staged at the Sydney Convention and Exhibition Centre 13–16 August, attracted over 2300 delegates. The meeting commenced with an indigenous Welcome to Country ceremony, providing the prelude to an action-packed program of symposia, breakfast theme sessions, free communications, mini orals, posters and workshops. This year, ISHR was particularly delighted to welcome several invited speakers well known on the ISHR International scene - David Eisner (University of Manchester), Elizabeth ‘Tish’ Murphy (NIH Bethesda), and Christine Seidman (Harvard, Boston). All attracted robust attendance to the Basic Mechanisms stream and made excellent contributions to a number of sessions – both from the podium and from the pews.

The Basic Science Lecture was presented by Michael Clark (University of Tasmania, Australia) on the topic: ‘Microvascular dysfunction and diabetes: from animal models to human studies’, highlighting a novel action of insulin on microvascular perfusion. Beyond the 8 parallel streams of themed Symposia that ran from Friday to Sunday, there was plenty of opportunity at the meeting for delegates to present their research at poster sessions (including “electronic posters” that could be continuously accessed) and, for the first time, as five-minute mini-orals. These ‘speed science’ sessions were very popular, and proved an excellent way of quickly gaining a research snapshot – and left many of the presenters enthusiastically breathless!

Putting together such a busy and successful meeting was the product of more than a year’s hard work. In particular, the efforts of Peter Macdonald and Chris Semsarian, as Chairs of the Local Organizing and Scientific Programme Committees, have been pivotal. Our ISHR appointees to these committees (David Allen and Lea Delbridge) also worked hard behind the scenes and were given plenty of scope by the Chairs to shape up the ISHR content.

ISHR strongly supports the participation of the younger members at our meetings, providing student travel awards, and including an ISHR Early Career Researcher Workshop in the programme. For 2009, this workshop was organized and chaired by James Bell and Nader Ghaffari, the newly appointed ISHR Council ECR representatives. Tish and David (as special guests) were persuaded to be panelists in a discussion about ‘Finding the right post-doc position’ and had some wise, practical (and humorous) insights to offer which were much appreciated.

A number of Student prizes are awarded annually, the most prestigious of which is the Student Investigator Oral Presentation Award. This year, an independent panel of five judges shortlisted four applicants for the award, based on assessment of submitted abstracts. The winner ($1000) was Helena Viola (School of Biomedical, Biomolecular and Chemical Sciences, University of Western Australia). Her presentation was titled ‘Evidence for mitochondrial complex III as source of superoxide production after transient exposure to H_2O_2’. The runner-up: ($500) was Steven Weiss (John Curtin School of Medical Research, Australian National University) who presented his work ‘Riluzole reduces ventricular arrhythmias and myocardial damage in an open-chest model of ischemia reperfusion injury’ at the Welcome to Country ceremony.
The talented ISHR Student Investigator Oral Prize finalists (left to right) Steven Weiss, Nicholas Lam, Elisha Hamilton and Helena Viola (winner).
Death and Senescence, both are problems - p53 causes Cardiovascular and Metabolic Diseases

DNA damage induces cell death or cell cycle arrest as well as infinite proliferation of cells (1-3). A variety of molecules and factors can induce DNA damage, such as irradiation, ultraviolet light and anti-cancer drugs. Ischemia/reperfusion and many neurohumoral factors, including catecholamine and angiotensin II, can induce DNA damage by increasing reactive oxygen species. The heart rarely forms cancer, probably because cardiomyocytes have little ability to proliferate after birth. Instead, cardiomyocytes show apoptosis or senescence in response to DNA damage, which may result in heart failure. Cell senescence can also cause various cardiovascular and metabolic diseases such as atherosclerosis and diabetes.

p53 Induces Heart Failure (4-7)
Pressure overload initially induces cardiac hypertrophy to reduce wall stress and maintain normal cardiac function. At this stage, vascular growth was enhanced in the heart by hypoxia-inducible factor-1 (Hif-1)-dependent induction of angiogenic factors. However, sustained pressure overload induced an accumulation of p53, at least in part by DNA damage, which inhibited the Hif-1 activity. Inhibition of cardiac angiogenesis enhanced hypoxia, resulting in systolic dysfunction. Conversely, promoting cardiac angiogenesis by introducing angiogenic factors or by inhibiting p53 accumulation developed hypertrophy further but restored cardiac dysfunction under chronic pressure overload. These results suggest that the tumor suppressor protein p53 has a crucial function in the transition from cardiac hypertrophy to heart failure by inhibiting angiogenesis (4).

Little attention has been paid to the DNA damage response of cardiomyocytes possibly because cardiac cancer is very rare. Doxorubicin is known to have cumulative dose-dependent cardiotoxicity. Doxorubicin, an anti-cancer drug, induced p53 accumulation via oxidative stress-induced DNA damage of cardiomyocytes in vitro and in vivo. Doxorubicin-induced contractile dysfunction and myocyte apoptosis were attenuated in heterozygous p53 deficient mice and cardiac-restricted Bcl-2 transgenic mice, suggesting that myocyte apoptosis plays a central role downstream of p53 in doxorubicin cardiotoxicity (5). The results of two studies suggest that p53 causes heart failure by inhibiting angiogenesis and inducing apoptosis of cardiomyocytes, but there might be other mechanisms by which p53 is involved in the development of heart failure. It has been reported that p53 regulates mitochondrial respiration with secondary changes in glycolysis (6) and that p53 induces inflammation such as upregulation of inflammatory cytokines (7).

p53 Induces Atherosclerosis (8-12)
Ras has been reported to induce premature senescence of various types of cells including vascular smooth muscle cells (8, 9). As one of the many activators of Ras, angiotensin II also induced premature senescence of human vascular smooth muscle cells with enhanced expressions of proinflammatory cytokines and adhesion molecules via the p53/p21-dependent pathway in vitro and in vivo. Loss of p21 markedly ameliorated the induction of proinflammatory molecules by angiotensin II and prevented the development of atherosclerosis (10), suggesting that angiotensin II promotes atherosclerosis by induction of vascular cell senescence via upregulation of p53.

Many molecular mechanisms have been suggested to contribute to human aging and its associated diseases. Recent genetic analyses have demonstrated that reduction-of-function mutations in the signaling pathway of insulin/insulin-like growth factor-1 (IGF-1)/phosphatidylinositol-3 kinase (PI3K)/Akt (also known as protein kinase B) extend the longevity of the nematode Caenorhabditis elegans (11). Although the signaling pathway of insulin/phosphatidylinositol-3 kinase/Akt is known to play a critical role in glucose metabolism and survival of mammalian cells, constitutive activation of Akt promoted senescence-like arrest of cell growth via the p53/p21-dependent pathway (12). Akt inactivated a forkhead transcription factor, FOXO3a, which influenced p53 activity by upregulating the level of reactive oxygen species. In patients with type 2 diabetes and metabolic syndrome, blood insulin levels are elevated because of the increased resistance to insulin in the liver and skeletal muscle. The elevated insulin may activate phosphatidylinositol-3 kinase/Akt signaling in vascular cells, which may lead to atherosclerosis (12). In diabetes, another candidate for vascular injury is high... (continued on page 14)
the news bulletin of the international society for heart research

(continued from page 13)

glucose. Treatment of human endothelial cells with high glucose decreased expression of an NAD(+)-dependent deacetylase SIRT1, a mammalian homolog of Sir2 (13). Downregulation of SIRT1 activated p53 by increasing its acetylation. Introduction of SIRT1, or disruption of p53, inhibited high glucose-induced endothelial senescence and dysfunction. Likewise, activation of SIRT1 prevented the hyperglycemia-induced vascular cell senescence and thereby protected against vascular dysfunction in mice with diabetes (13). Expressions of p53 were increased in the limbs of mice with diabetes and ischemia. p53 also inhibited angiogenesis at least partly by upregulating the axon-guiding molecule semaphorin3E, which inhibited the action of VEGF (14).

p53 Causes Diabetes (15)

Excessive calorie intake led to the accumulation of oxidative stress in the adipose tissue of mice with type 2 diabetes and promoted senescence-like changes, such as increased activity of senescence-associated β-galactosidase, increased expression of p53 and increased production of proinflammatory cytokines. Inhibition of p53 activity in adipose tissue markedly ameliorated these senescence-like changes, decreased the expression of proinflammatory cytokines and improved insulin resistance in mice with type 2 diabetes. Conversely, upregulation of p53 in adipose tissue caused an inflammatory response that led to insulin resistance. Adipose tissue from individuals with diabetes also showed senescence-like features. These results show a previously unappreciated role of adipose tissue p53 expression in the regulation of insulin resistance, and suggest that cellular aging signals in adipose tissue could be a new target for the treatment of diabetes (15).

Cells respond to DNA damage by activation of various protein kinases, such as ATM, ATR, CHK1 and 2, which reduce cyclin-dependent kinase activity by various mechanisms, some of which are mediated by the activation of p53 (2, 3, 16). Accumulation of DNA damage can be an important cause of cardiomyopathy. First, cardiomyocytes exhibit high mitochondrial respiration and thus produce lots of reactive oxygen species that can damage mitochondrial and nuclear DNA. Second, cardiomyocytes are vulnerable to DNA damage because of the limited capacity for cell replacement after birth. Furthermore, cardiomyocytes, being in G0, cannot repair double-strand breaks by homologous recombination and must use error-prone non-homologous end-joining (17). Although the proliferative ability of cardiomyocytes is very limited, the transcriptional activity is very high. Since oxidative DNA damage can block transcription, various stresses that increase reactive oxygen species can induce cardiomyocyte degeneration and death (18). The upregulated p53 also induces apoptotic cell death and cellular senescence. Accumulating evidence has suggested that loss of cardiomyocytes may cause dysfunction, although the mechanisms are elusive. Expression patterns of various proteins, such as contractile proteins and metabolism-related proteins, may be changed in senescent cardiomyocytes, or inflammatory cytokines may be upregulated in the senescent heart.

Aging, as well as hypertension and diabetes, causes atherosclerosis. Vascular cell senescence may be a common cause of atherosclerosis by enhancing expression of inflammatory cytokines and adhesion molecules (19). Ross has mentioned that atherosclerosis is an inflammatory disease (20). Vascular cell senescence may cause atherosclerosis by inducing inflammation of vessels. DNA damage, p53 and cellular senescence could be novel targets of cardiovascular and metabolic diseases (ref. 2, Figure).

References


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We are pleased to present this article by Dr Issei Komuro as the third in our series of articles written by members of the ISHR International Council.

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