I was born on April 11 in Berlin, Germany. After obtaining the general qualification for university entrance, I went to medical school, first in Halle (Saale) and thereafter in Magdeburg. These cities are situated in the former East Germany (the German Democratic Republic). When I was 19 years old, I met Wolfgang Schaper, a student in Medical School who was 3 years my senior. We married in 1958 and have been married to each other ever since (Fig. 1). Wolfgang started to work in a hospital in Magdeburg and, therefore, I changed medical schools. In 1959, our daughter Susanne was born. In 1960, we left East Germany and moved to Belgium where Wolfgang was employed by the Janssen Research Foundation in Beerse. I finished medical school in Düsseldorf/Germany in 1961 and started to work in the Janssen laboratory. I worked half-time in order to take care of our three children, Susanne and...

After my training in electron microscopy at the University of Antwerp, I started to carry out my own research projects. My research was concerned with the collateral coronary circulation in experimental animals, my husband’s main research interest, to which I could contribute by studying the structural changes in these vessels. In collaboration with Marcel Borgers, I published several papers on the structure of collateral vessels. In 1976, we with Professor F. Hehrlein, Giessen) and in animal myocardium (in collaboration with Professor J. Bretschneider, Göttingen). We calibrated and standardized the ultrastructural characteristics of ischemic injury in global and regional ischemia. The morphological changes were compared with biochemical and functional data and reversible versus irreversible injury was identified. This allowed the testing of numerous cardioplegic solutions in both the experimental and clinical settings. We finally found the optimal cardioplegic solution for open-heart surgery, the so-called “Bretschneider solution”, which, in combination with local hypothermia, is widely used nowadays in clinical practice.

In 1976, we were the first to demonstrate that monocytes are intimately involved in vessel growth.

In 1972, we moved to Bad Nauheim, Germany, where Wolfgang became Director of the Max-Planck-Institute for Experimental Cardiology. This was a major change because we had to leave our beloved Belgium and our many friends there, we had to adapt to a different system professionally and the children had to change languages in school. During our first months in Germany I was more a teacher in the German language than a scientist, but in November 1972 I started to work again, as head of the Department of Cardiovascular Cell Biology at the Max-Planck-Institute in Bad Nauheim.

In 1980, I defended my Ph.D. thesis in Experimental Cardiology at the University of Giessen. In 1982-1983, Wolfgang and I spent a sabbatical year at Duke University, Durham, North-Carolina, together with our youngest son, Martin, who attended his last year of high school there. Dr Robert B. Jennings was our gracious host, and he and I collaborated on the problem of reperfusion injury. Dr Joachim Sommer greatly impressed me with his single cell experiments and his scientific wisdom. After we came back to Germany, I worked on the effects of ischemia/reperfusion in animal models of myocardial infarction, preconditioning and infarct size reduction. The major conclusion from this work was the sobering fact that a true reduction of infarct size is impossible to obtain; the only beneficial effect of any drugs or methods is a delay in the occurrence of cell death. In addition, Wolfgang and I contradicted the common opinion that reperfusion after ischemia results in aggravation of cellular injury, a belief widely held even today.

My main interest, however, was in the correlation between structure and function in human myocardium. Our group was the first to describe structural defects in failing human hearts and to determine multiple factors involved in structural remodeling. We found that cellular degeneration finally resulting in cell death is a major event in all cardiac pathologies. The major characteristics are loss of contractile material and of the sarcomeric skeleton including titin and α-actinin (especially ACTN2, whereas ACTN-1 accumulates and is a marker of degeneration), combined with an increase of the cytoskeletal elements desmin and the microtubular network. It was hypothesized that loss of the contractile machinery and related proteins, such as titin and α-actinin, may be the first and decisive event initiating an adaptive increase in the cytoskeleton and membrane-associated components such as dystrophin and vinculin. Connexin43 and related proteins of the intercalated disc were elevated in compensated hypertrophy, but diminished showing a heterogeneous distribution in decompensated hypertrophy, which may play a maladaptive role culminating in heart failure and ventricular arrhythmias. Myocyte and nuclear hypertrophy and an increased synthetic rate of DNA and the splicing factor Sc-35 were interpreted as compensatory, but insufficient, mechanisms. Fibrosis is the other key event in diseased human myocardium, occurring as either reactive or replacement fibrosis and very often as both. Fibrosis is stimulated by subcellular degeneration. There are subtle differences in the morphology of the
different pathogenetic entities, e.g. in pressure overload the myocytes enlarge in width and length whereas in volume overload the cells are slender but very long. We studied the cardiac structure in hypertrophy due to pressure and volume overload, and the ischemic myocardium and the tissue remote from the ischemic area in dilated as well as in hypertrophic cardiomyopathy, and always came to the same conclusion. In 1991, we published a comprehensive, frequently cited, study in Circulation on the impairment of the cardiac ultrastructure in heart failure.

In 2003, we described in Circulation the correlation between cardiac structure and function during the progression from compensated to decompensated hypertrophy in patients with aortic valve disease. We defined the structural correlate of heart failure: severe cellular degeneration and an increased rate of myocyte cell death, reduction of capillary density, as well as a several-fold elevated degree of fibrosis. The same is true in human hibernating myocardium; already in 1997, a study was published which showed that adaptation to chronic ischemia is incomplete resulting in cellular degeneration and fibrosis, and that, from a clinical point of view, this situation is dangerous. Stefan Hein was the first author in the hypertrophy study and Albrecht Elsässer investigated hibernating myocardium; both of them are clinicians. Sawa Kostin, my long-term and very effective collaborator, was coauthor of many publications and first author of the connexin studies from my lab. He and I, in continuation of the work by Knaapen published in 2001, propagated in 2003 a third type of cell death that exists apart from the commonly described ischemic and apoptotic cell death; namely autophagic cell death involving the proteasome system and ubiquitin. These 4 papers together have been cited more than 1000 times in other publications.

We were thus the first to describe the structural correlates of heart failure and to determine multiple factors involved in structural remodeling. These studies were not only carried out in tissue from human patients, but the findings were validated and confirmed by studies in experimental animals and in cell cultures.

Apart from this work, we also investigated the mechanisms of cellular hypertrophy with special interest in the role of titin as well as the development of fibrosis with emphasis on the role of metalloproteinases. I have published more than 195 peer-reviewed articles in addition to numerous abstracts and book chapters, and I have been invited to present our work at numerous national and international conferences. I serve in the Editorial Board of a number of scientific journals, and I received several prizes and honorary memberships, but a description of these is beyond the limits of this article.

I usually had a group of about 10-12 postdocs and graduate students in addition to my four experienced and loyal technicians. We all enjoyed the international atmosphere created by students from all over the world, as can be seen in Figure 2.

Apart from my scientific work, I was active in the organization of the ISHR, first as Secretary General of the European Section from 1981-1992; thereafter, from 1992-1995.
I have no message to give, no advice to dispense. But I can say that a life occupied with the sciences and the arts was a lot of fun, yet mixed with disappointments. There was the pleasure of trying something new, the frustration of not being able to succeed at times, the discomfort caused by political defeats, the failure for not being recognized for what you have done and what you could do. But foremost, there were the pleasures of living – of seeing the world’s beauty; its lakes, mountains, stars, laughter and tears. There was the fallacy of believing that you could make a difference in the course of events, while in reality you were but a puff of smoke in an endless universe. In science we often try to show little emotion, but emotion is an important factor in our relationship to life’s progression.

So much has been written about science – how it brings satisfaction and rewards. Much less is said about its dark side: the search for funds, the failures and disappointments, the political machinations. But the measure of a man is not what he does when all is smooth, but what he can do in the time of defeat, adversity and neglect. The behavior of a person during adversity shows his real stuff. Anyway, it is all over in no time — para fuera.

Richard J. Bing, M.D.
Dear Colleagues,

This is my last column as the president of the ISHR. It has been an honor and a pleasure to serve you as your president for the past three years, and to be part of this remarkable and unique society. I say “unique” because I believe the ISHR has its own personality, which sets it apart from other major scientific societies. Its strength lies precisely in its smallness - in its quasi “mom and pop” business model. We have only one paid employee (Executive Secretary, Leslie Anderson Lobaugh). We don’t have an army of staff persons, volumes of rules and regulations, or cohorts of advisors, consultants, lobbyists, subcontractors, lawyers, and the like. We don’t even have a building. (Amazingly, the largest international society in the world dedicated to basic cardiovascular science has no headquarters.)

But we have what matters. We have a legion of enthusiastic, hard-working, dedicated, wonderful volunteers who are united in their passion for the mission of the ISHR. They make our society work better than any paid staff would. And we have a personal touch, a friendliness, a spirit of camaraderie that you will not find in any other major cardiovascular society. We have not become victims of the ravages of political correctness, at least not yet. We have kept a sense of humor, a feeling of personal connectedness, a team spirit that is obvious if you were to attend our Section meetings, our World Congresses, our Council meetings, anything. In short, we are a family. It’s absolutely remarkable that more than 40 years after the founding of our society in 1968, we have managed to keep that personality that permeated the original organization. I believe that this is our strength, this is what makes us different from everybody else, and this is what we should try to preserve as jealously as we can.

I have been a member of the ISHR since 1984. For 26 years I have been involved in many different capacities, and I have done it with passion and energy, always trying my best, because I believe the ISHR is a vibrant organization that plays a unique and very useful role in the cardiovascular scientific community. This Society has been a big part of my life. I am grateful to it for giving me so many opportunities to contribute.

As I leave the helm of the ISHR, I am gratified to see that it has changed for the better and, in all likelihood, will continue to change for the better in the foreseeable future. Too many times, for too many years, the Society has fallen prey to the personal agenda of individuals who have used it for their own personal aggrandizement or scientific survival. We all know about these things. We all have witnessed what is commonly referred to as “politics” (a euphemism for much worse appellations). Of course, using the ISHR in hopes of keeping oneself afloat in science is not only futile (it really does not work) but, more importantly, damaging to the image, credibility, and reputation of the Society as a whole. Fortunately, in recent years the winds have changed. After years of feuding and squabbling, the Sections have finally come together. And the current leadership of both the International Section and the Regional Sections is composed of individuals who have scientific credibility and are not committed to politics above all.

My recommendations for future leaders are simple. Always put science first. When you choose award winners, members of Councils, committee members, etc., always think science above anything else. Don’t cave in to the obtuse bigotry of political correctness. Remember that the best person for a job is... the best person for that job – this is a very obvious concept but, sadly, one that is being increasingly violated in our decadent culture. Try to preserve the ISHR personality. Keep the Society accessible to young investigators and outsiders. This accessibility makes the ISHR strong. Above all, always do what is best for science, not for people’s careers or egos.

In leaving my post, I am pleased to see that the ISHR is in much better shape than just a few years ago. I see a bright future ahead, a time in which the overriding imperative of ISHR leaders will be science (as I advocated in my President’s Inaugural
Address in Bologna on June, 22, 2007), not politics. I am particularly happy to leave the Society in the capable hands of Masatsugu Hori. I am certain he will run the Society with wisdom, equanimity, and integrity. I am also very happy that Rick Moss has been appointed Secretary General and Tish Murphy has been reappointed Treasurer. Matt, Rick, and Tish are a dream team - they epitomize the kind of leaders that our Society needs and that will move the ISHR forward. They are not only outstanding investigators but also passionate volunteers and wonderful human beings with the ability to work together, seek consensus, and transcend personal politics. I wish them and the Society the best. The ISHR is in very good hands.

I would like to conclude this column with some thoughts about research, a research career, and life - the result of years of personal experiences and reflections - which I hope will be useful to the readers.

1. Science is easy, people are difficult.
2. Motivation cannot be taught or inculcated. Either you have it or you don’t.
3. If something is worth doing, it’s worth doing well. Whatever you do, do it well or don’t do it.
4. Be persistent and perseverant.
5. Follow your passion.
6. If you don’t know what you want in life, you’ll never get it.
7. Always stay focused – focus is absolutely critical, particularly in research. Focus is what enables you to become a leader. Don’t jump from one thing to another.
8. Don’t expect immediate gratification; expect frustration. Remember: Things always take more time and are more difficult than you think.
9. Success is 10% inspiration and 90% perspiration. The single most important quality to achieve success is, by far, hard work. Intelligence is much less important. Remember one of the greatest truisms in life: “Even a genius will be a failure if he’s lazy”. The world is full of very smart people who never made it because they did not work hard. So, above all, work hard.
10. Another major determinant of your success will be emotional – i.e., your ability to make people feel good. In fact, your social intelligence will be more important than your cognitive intelligence (these two intelligences are completely independent of one another and thus can be totally disassociated).
11. Be organized. This is crucial.
12. Your success will also be determined by your communicative skills. You are judged by the way you speak and write (at times, this is even more important than what you actually say).
13. The secret in life is to be able to turn a bad thing into a good thing – to turn a stumbling block into a stepping stone.
14. In research, as well as in academia in general, the best predictor of future performance is past performance. If you wish to know what someone will do in the next five years, you can get a fairly good idea by looking at what he has done in the last five years.
15. We are drowning in a sea of paperwork and red tape, and every year there is more of it.
16. Being succinct takes time, if you want to do it well (i.e., if you want to avoid superficiality, errors, and distortions).
17. How many people do you know who really work?
18. If you can’t explain a scientific or medical concept to your plumber, you don’t quite understand it (this is known as the plumber’s principle).

And, finally, don’t forget Aristotle’s poignant, sublime words: “Without friends, nobody would choose to live, even if he had everything else”.

Roberto Bolli, M.D.
We organized the 26th Annual Meeting of the International Society for Heart Research - Japanese Section in Sapporo, Hokkaido. This was the second time we held the Annual Meeting in Hokkaido; in July of 1997, the 14th Annual Meeting was held in Asahikawa.

The purpose of this conference was to bring together the most exciting advances in both basic and clinical cardiovascular research, including advances in the study of ischemic heart disease and congestive heart failure. This program was also unique in that talks addressing fundamental understanding and clinical application were arranged in a coordinated fashion. This served to emphasize the smooth transition between basic investigation and clinical practice. This annual meeting was attended by professionals involved in delivering cardiovascular care, including physicians, scientists, and assistants. We had 4 symposia, 2 special lectures, 2 luncheon seminars and a YIA session. The program included the following presentations:

Symposium 1: Molecular Pathophysiology and New Strategy in Heart Failure (i: “Protein Phosphatase Inhibitor-1 can augment a protein kinase A-dependent increase in the SR Ca$^{2+}$ loading without changing the SR Ca$^{2+}$ release” by Hiroshi Satoh; ii: “Cardiac fibroblasts are essential for the adaptive response of the heart to pressure overload” by Norifumi Takeda; iii: “The in vivo Role of IkB kinase b (IKKb)/NF-kb signaling pathway in the heart” by Shungo Hikoso; iv: “Intertissue interactions between the myocardium and the vasculature regulate cardiac growth, coronary angiogenesis, and contractile function” by Ichiro Shiojima; v: “Myocardial regeneration therapy by cell sheet technology for severe heart failure” by Shigeru Miyagawa; and vi: “Gap junction remodeling is an important arrhythmogenic substrate during development of heart failure” by Tomoko Ohkusa).

Symposium 2: Mitochondria, Cytoprotective signaling, and Cardiomyocyte protection. (i: “Mitochondrial oxidative stress induces an integrated stress response in the heart” by Motoaki Sano; ii: “Caloric restriction primes the mitochondria for ischemic stress: possible involvement of mitochondrial protein deacetylation with caloric restriction” by Ken Shimamura; iii: “Modulation of mitochondrial permeability transition pore by CaM/CaMKII and GSK3β” by Hideki Katoh; and iv: “Impairment of pro-survival signaling in the myocardium under metabolic and mechanical stress: roles of GSK-3β and the mitochondrial permeability transition pore” by Takayuki Miki).

Symposium 3: Bridge Over the Basic and Clinical research in Cardiovascular Medicine (i: “Sphingosine 1-phosphate is a bioactive lipid that confers high-density lipoprotein with vasculoprotection mediated by endothelium-dependent vasodilation” by Satoshi Fujii; ii: “G-CSF therapy for acute myocardial infarction: studies of animal experiments give valuable hints to clinical trials” by Hiroyuki Takano; iii: “Heart failure therapy that targets nuclear signaling pathway in cardiomyocytes – from bench to bedside” by Tatsuya Morimoto; iv: “Allosteric modulation of hemoglobin is the new therapeutic target for improving exercise capacity in patients with chronic heart failure” by Toshihiro Takeda; v: “Clinical and experimental gene transfer for coronary intervention - from our seven-year clinical experiences to experimental non-viral siRNA transfection” by Junichi Suzuki; and vi: “Essential role of autophagy to maintain cardiac function in response to hemodynamic stress and in senescence”
Symposium 4: *A New Era of Renin-Angiotensin-Aldosterone System* (i: “Effects of direct renin inhibition for survival after myocardial ischemia with renal failure in mice” by Masahito Ogawa; ii: “Angiotensin II (AT2) receptor antagonizes AT1 receptor-derived signaling via PKC activity in the signaling endosome” by Masumi Tsuda; iii: “Molecular mechanisms of AT2 receptor as a dominant negative receptor against AT1 receptor-induced cell signaling” by Shinichiro Miura; iv: “Agonist-independent activation of angiotensin II receptor in the pathogenesis of left ventricular remodeling” by Hiroshi Aka-zawa; and v: “Cyclophilin A promotes vascular oxidative stress and accelerates development of angiotensin II-induced aortic aneurysms” by Kimio Satoh).

The Keynote Lecture (“Mitochondrial ATP-binding cassette protein-1 (mABC1) is involved in cytosolic iron-sulfur protein assembly”) was presented by Dr Hossein Ardehali from Northwestern University (Chicago, IL, USA). We also had a special lecture by Dr David A. Eisner, (University of Manchester, Manchester, UK) on the opening day of the meeting. The title of the lecture was “Calcium signaling in the heart in health and disease”. This session was chaired by Dr Masatsugu Hori (Osaka University), President of the ISHR. We also enjoyed the Keith Reimer Distinguished Lecture presented by Dr Elizabeth Murphy (NHLBI, NIH, Bethesda, MD, USA) on the second day of the meeting. The title of her lecture was “The role of SNO (S-nitrosylation) in cardioprotection”.

We had two luncheon seminars which were unique and exciting. The titles of the seminars were: “Luncheon Seminar 1: “The RAS blockade leads to anti-atherosclerosis”, and Luncheon Seminar 2: “The new strategy for primary and secondary prevention of ischemic cardiac disease in Japan”.

All registrants were enriched through the comprehensive programming and stimulating discussions. We would like to promote the scientific basis for the practice of cardiology, to foster the exchange of information among cardiovascular scien-

tists and to increase public awareness with respect to cardiovascular health and disease. From the 1970s, Prof. Yasuda from Hokkaido University, Prof. Iimura from Sapporo Medical University, and Prof. Onodera from Asahikawa Medical College have promoted cardiovascular science in Hokkaido. Their outstanding work laid the foundation, and now we must do our part to continue to advance the understanding of cardiac health and disease.

Dr Hideaki Kawaguchi
Chairman, 26th Annual Meeting of the Japanese Section
Department of Laboratory Medicine,
Hokkaido University Graduate School of Medicine
Dr GERD HASENFUSS is Professor of Medicine, Chief and Chair of the Department of Cardiology and Pneumology and Chief of the Heart Center at the University of Goettingen in Germany. He is active as a clinical cardiologist, researcher and teacher and has won several teaching awards. Dr Hasenfuss received his MD from the University of Freiburg, Germany, in 1981, and finished his clinical training in internal medicine and cardiology in 1988. Thereafter, he became a visiting professor at the Department of Physiology and Molecular Biophysics at the University of Vermont and worked together with Dr Norman Alpert. He obtained his venia legendi (Habilitation) from the University of Freiburg in 1990. From 1994 -1998 he had a Heisenberg Fellowship of the German Research Foundation.

Dr Hasenfuss’s main research interest is the pathophysiology and treatment of heart failure, including both basic research as well as clinical studies in patients. Within the field of heart failure, he began his research career with studies on cardiac energetics and the energetic consequences of inotropic treatment interventions. A particular focus has been studies on excitation-contraction coupling and contractile protein function in isolated failing and non-failing human myocardium. His studies in isolated myocardium, as well as in patients, showed that frequency-potentiation of contractile performance (force-frequency relation) is absent or inverted in the failing human heart. In subsequent studies, he and his group showed that the altered force-frequency relation results from disturbed excitation-contraction coupling due to loss of frequency-dependent upregulation of sarcoplasmic reticulum (SR) calcium content. The latter could be attributed to a decreased expression of sarcoplasmic reticulum calcium pump (SERCA), increased expression of the sarcolemmal sodium-calcium exchanger and increased SR leak. To develop new therapeutic options to treat heart failure, he recently focussed his scientific interest onto stem cell cardio-biology. In search of adult multipotent stem cells, his group discovered the spermatogonial stem cell of mouse testis as an embryonic stem cell-like pluripotent cell. Dr Hasenfuss and his group showed that spermatogonial stem cells or multipotent adult germ line stem cells have the potential to differentiate into all three germ layers; cardiac differentiation occurred in vivo and under in vitro conditions. Currently, the group is searching for culture conditions to transfer the technique to human tissue.

Dr Hasenfuss is a Fellow of the International Society for Heart Research, the American Heart Association and the European Society of Cardiology. He has received several research awards, and is a member of the Academy of Science of Goettingen, Germany. He is a member of more than 10 editorial boards, including European Heart Journal and Circulation Research. Dr Hasenfuss serves on the Review Board of the German Research Foundation (Fachkolleg). He is a member of the Board of Heart Failure Association and a member of the Basic Cardiovascular Science Council of the European Society of Cardiology. Dr Hasenfuss is organizing several national and international research networks including EUGeneHeart.
Honorary Life President:
Richard J Bing, USA

President:
Masatsugu Hori, Japan

President-Elect:
Metin Avkiran, UK

Past President:
Roberto Bolli, USA

Secretary General:
Richard Moss, USA

Treasurer:
Elizabeth Murphy, USA

Journal Editor:
David Eisner, UK

Bulletin Editor:
Leslie Anderson Lobaugh, USA

Council:
Donald M Bers, USA
Kieran Clarke, UK
Lea Delbridge, Australia
Thomas Eschenhagen, Germany
Keiichi Fukuda, Japan
Sian Harding, UK
Ru-Tai Hui, China
Tohru Izumi, Japan
Lorrie Kirshenbaum, Canada
Issei Komuro, Japan

Newly Appointed Fellows of the ISHR

David G. Allen
Sydney, Australia

Mark Anderson
Iowa City, IA, USA

Thomas Eschenhagen
Hamburg, Germany

Keiichi Fukuda
Tokyo, Japan

Robert Gottlieb
San Diego, CA, USA

Henk Granzier
Tucson, AZ, USA

Sian Harding
London, UK

Joseph Hill
Dallas, TX, USA

Steven Houser
Philadelphia, PA, USA

Daniel P. Kelly
Orlando, FL, USA

Lorrie Kirshenbaum
Winnipeg, MB, Canada

Walter Koch

Issei Komuro

Cam Patterson

Pei-pei Ping

Howard Rockman

Ajay Shah

Karen Sipido

Charles Steenbergen

Susan Steinberg

Jennifer Van Eyk

Evangelia Kranias, USA
Masahiko Kurabayashi, Japan
Cam Patterson, USA
Burkert Pieske, Austria
David Saint, Australia
Ranier Schulz, Germany
Mark Sussman, USA
KK Talwar, India
Martin Vila-Petroff, Argentina
Jennifer Van Eyk, USA
Rui-Ping Xiao, China

Philadelphia, PA, USA
Chiba, Japan
Chapel Hill, NC, USA
Los Angeles, CA, USA
Durham, NC, USA
London, UK
Leuven, Belgium
Baltimore, MD, USA
New York, NY, USA
Baltimore, MD, USA
DR DONALD BERS is the Joseph Silva Chair for Cardiovascular Research, Distinguished Professor and Chair of the Department of Pharmacology at the University of California, Davis School of Medicine. He received his doctorate in Physiology from UCLA in 1978. He did a postdoc at the University of Edinburgh, then returned to UCLA and UC Riverside where he rose to Professor. He was Chair of Physiology at Loyola University Chicago from 1992-2008 before moving to UC Davis. He sits on the editorial boards of: Circulation Research, Journal of Molecular and Cellular Cardiology (as Assoc Ed) and Cell Calcium. He has served in leadership roles in the AHA, Biophysical Society, American Physiology Society, Heart Failure Society of America and International Society for Heart Research (now President of NA Section), as well as on grant review panels at NIH and AHA. He is a Fellow of the AHA, ISHR and Biophysical Society. He is the Principal Investigator of an NIH Program Project Grant and MERIT award, author of more than 250 research articles, and a definitive and renowned single-author book Excitation-Contraction Coupling And Cardiac Contractile Force. Dr Bers has also mentored dozens of Ph.D. students and postdoctoral fellows.

Dr. Bers’ research focus is on Ca²⁺ regulation in cardiac myocytes as a nodal control point in cardiac electrical activity, excitation-contraction coupling, energetics and, recently, excitation-transcription coupling. Work in his lab has focused on the fundamental aspects of numerous ion channels and transporters involved in cardiac function, and on how these interact dynamically in the myocyte environment to regulate cardiac electrophysiology and contractility, by combining quantitative biophysical, molecular and cellular approaches. His comprehensive and rigorous work has formed the foundation of our modern understanding of the detailed contribution and regulation in intact cardiac myocytes of Ca current, Na/Ca exchange, SR Ca uptake and release, mitochondrial Ca uptake and Na/K-ATPase. His integrative perspective on quantitative aspects of how cardiac myocytes work is widely appreciated.

His group also studies what goes wrong with these systems in the setting of heart failure, and how that contributes to contractile dysfunction and arrhythmogenesis in heart failure, work that helps to identify potential targets for therapeutic intervention. His group also develops computer models to synthesize the combined function of many cellular channels, transporters and their regulation. These serve as educational tools, help predict the behavior of this complex system and aid in sharpening new experimental hypotheses to enrich our understanding of cardiac function. Dr. Bers has also actively collaborated in research with many other groups, and has contributed to the synergistic progress of cardiac research.

**Previous Award Winners**

- 2003 Piero Anversa
- 2004 David Kass
- 2005 Edward Frohlich
- 2006 Evangelia Kranias
- 2007 Joanne Ingwall
- 2008 Howard Rockman
DR ELIZABETH MURPHY is Head of the Cardiac Physiology Section in the Translational Medicine Branch at the National Heart, Lung and Blood Institute. She received her PhD from the University of Pennsylvania in Biochemistry in 1980, followed by postdoctoral studies in Physiology at Duke University. In 1984, Dr Murphy was appointed a Research Assistant Professor in the Department of Physiology at Duke University. In October, 1984, she joined the National Institute of Environmental Health Sciences, National Institutes of Health as a Staff Scientist. She was tenured in 1990, and continued at the National Institute of Environmental Health Sciences as Head of the Cell Biology Section in the Laboratory of Signal Transduction until she moved to the National Heart, Lung, and Blood Institute in 2006.

Dr Murphy received the Richard Bing Young Investigator Award in 1983. She is an Associate Editor for the Journal of Molecular and Cellular Cardiology, Senior Guest Editor for Circulation and Consulting Editor for Circulation Research. She also serves on the editorial board of the American Journal of Physiology. She is a Fellow of both the ISHR and the AHA. She served as a member of the Electrical Signaling, Transport and Arrhythmias NIH Study Section from 2004-2008, and as a member of Cardiovascular A Study Section from 1994-1998. She has served on a number of American Heart Association committees including the National Research Committee (2000-2005), and as a member of the Leadership Committee of the Basic Cardiovascular Science Council (2000-2004; 2006-2008). Dr Murphy served as Secretary of the American Section of the International Society of Heart Research from 2003-2009. She is currently President-Elect of the American Section of the International Society for Heart Research and a member of the International Council of the International Society for Heart Research.

Dr Murphy’s research is focused on ionic and energetic alterations in cell death and cardioprotection, and the signaling pathways that control these events. She has co-authored more than 150 papers. Work by her and her collaborators showed that the cardioprotective effect of the sodium-proton exchange inhibitors, such as amiloride, involved attenuating the rise in sodium and calcium during ischemia and reperfusion. Her lab further demonstrated that stress induced protection, termed preconditioning, also reduces the rise in Na+ and Ca2+ during ischemia. Over the years, her lab has published a number of critical studies examining the role of ion channel transporters such as the sodium proton and sodium-calcium exchangers in ischemia and reperfusion injury. Dr Murphy has also made important contributions in the development of calcium and magnesium indicators and holds a patent for a fluorescent calcium indicator. Her recent work has focused on the role of mitochondria in cell death and cardioprotection.

**The Keith Reimer Distinguished Lecture 2009**

**The Role of SNO (S-nitrosylation) in Cardioprotection**

**Honored Speaker: Dr Elizabeth Murphy**

**(December 2009; Sapporo, Japan)**

*Previous Award Winners*

- 2002 Roberto Bolli
- 2003 Gerd Heusch
- 2004 John Solaro
- 2005 Masao Endoh
- 2006 Garrett Gross
- 2007 Eduardo Marban
- 2008 David Eisner
IDENTIFICATION OF HES1 AS A REGULATOR OF CARDIAC PROGENITOR CELLS DURING HEART DEVELOPMENT

It was a great honor for me to be awarded the prestigious ISHR/SERVIER Research Fellowship in June 2008 in Athens. In 2007, I joined the group of Dr. Robert Kelly in the Developmental Biology Institute of Marseilles-Luminy as a postdoctoral researcher. My research project concerns the characterization of factors implicated in the regulation of cardiac progenitor cell fate during heart development; we recently uncovered the early role of the transcriptional repressor, Hes1, in the regulation of cardiac progenitor cells. It is a pleasure for me to present the research project that I have developed during the fellowship.

Heart Morphogenesis and Cardiac Progenitor Cells
Cardiac morphogenesis initiates with the formation of a cardiac crescent, at approximately mouse embryonic (E) day 7.5. Rapidly (E8.0), this cardiac crescent fuses at the midline and gives rise to the early heart tube, which undergoes a process of looping (E8.5) and rapid growth to generate the embryonic heart with well-defined future chamber regions (E10.5) 1. Recent studies on cardiomyocyte origins have revealed a more complete and accurate view of cardiogenesis, and demonstrate that the heart does not derive from a single source of progenitor cells but develops from two adjacent mesodermal populations 1. The first heart field is derived from anterior splanchnic mesoderm and gives rise to the cardiac crescent, early heart tube and ultimately to the left ventricle and part of the atria 2 (Figure 1). The second population of cardiac progenitors, termed the Second Heart Field (SHF), originates from the pharyngeal mesoderm contiguous to the cardiac crescent (Figure 1). It is characterized by the expression of diverse transcription factors and signaling molecules including the fibroblast growth factor 10 (Fgf10) 3 (Figure 2A), the LIM homeodomain transcription factor Islet1 (Isl1) 4 and the T-box transcription factor 1 (Tbx1, del22q11.2 syndrome candidate gene) 5. The Second Heart Field is defined by differentiation delay and continued proliferation and contributes to the early heart tube elongation through progressive addition of cells to the poles of the heart, in particular to the arterial pole of the developing heart tube and subsequently to the right ventricle and the outflow tract 3 (Figure 1).

An extracardiac cell population, the Cardiac Neural Crest (CNC), migrates from the dorsal neural tube into the outflow tract and plays a critical role in outflow tract morphogenesis and septation 6. In fact, interaction between CNC cells and SHF progenitors is essential for the regulation of SHF-derived cell addition to the heart tube.

Perturbations of signaling pathways controlling SHF development or CNC cell deployment result in failure of the outflow tract to correctly elongate and divide leading to congenital heart defects including overriding aorta, double outlet right ventricle and common arterial trunk, which are common components of human congenital heart disease 7. Despite recent advances in our understanding of SHF deployment, the molecular mechanisms maintaining SHF cells in a progenitor state and regulating their contribution to the elongating outflow tract remain poorly defined.

Hes1, a Novel Regulator of Second Heart Field Progenitor Cells
Recently, an enhancer trap transgene has
between two genes, chromosome 16 on the region B2-B4 the transgene integration site on mouse

- Using PCR and bioinformatic tools, we identified fluorescent complementary approaches, including trapped enhancer. Using diverse and

to identify the endogenous target of the transgene, we characterized the transgene integration site

- We identified new genes expressed in the SHF, which were characterized by

- Using diverse and complementary approaches, including fluorescent in situ hybridization, we identified the transgene integration site on mouse chromosome 16 on the region B2-B4 between two genes, Optic Atrophy 1 (Opa1), and Hairy/Enhancer of Split 1 (Hes1).

- The expression profiles of Hes1 and Opa1, together with those of 4 expressed sequence tags located between Hes1 and Opa1, were evaluated by whole mount in situ hybridization. Our results revealed that Hes1 is likely to be the endogenous target of the cis-regulatory elements trapped by the transgene (Figure 2B); in particular, Hes1 is expressed in pharyngeal mesoderm including the region of the Second Heart Field (Figure 2C).

- Taking into account the critical role of cardiac neural crest cells in heart development, we analyzed the impact of Hes1 deletion on this population and found a reduction of CNC numbers in the pharyngeal mesenchyme region of Hes1−/− embryos, suggesting that deployment of CNC cells is impaired in addition to decreased proliferation in the SHF.

- Hes1 encodes a basic-helix-loop-helix transcriptional repressor and regulates cell fate decisions in developing organs. Hes1 is known to play central roles in regulating cell proliferation and differentiation in multiple cell types and is required to maintain progenitor cells in an undifferentiated state. We investigated the role of Hes1 in heart development and particularly in SHF deployment. Analysis of Hes1 deficient embryos at E15.5 revealed that loss of Hes1 leads to arterial pole alignment anomalies including overriding aorta and ventricular septal defects (Figure 3). At earlier stages of development (E10.5), we observed that the outflow tracts of Hes1−/− embryos were shorter and straighter than those of control hearts, suggesting an alteration in SHF development (Figure 3).

- We next evaluated proliferation and differentiation in the SHF and demonstrated that SHF progenitor cells proliferation, but not differentiation, was impaired in Hes1−/− embryos. Hes1 controls the cell cycle through the transcriptional repression of cyclin-dependant kinase inhibitors such as p27Kip1 and p57Kip1. In order to investigate the molecular mechanisms by which Hes1 controls SHF progenitor proliferation, immunohistochemistry on micro-dissected tissues including the SHF region were performed. Our results demonstrated that loss of Hes1 leads to an expanded expression domain and upregulated expression of p27Kip1 expression (Figure 3).

- Taking into account the critical role of cardiac neural crest cells in heart development, we analyzed the impact of Hes1 deletion on this population and found a reduction of CNC numbers in the pharyngeal mesenchyme region of Hes1−/− embryos, suggesting that deployment of CNC cells is impaired in addition to decreased proliferation in the SHF.

- Our work demonstrates that loss of Hes1 affects two different cell populations critical for heart development, Second Heart Field progenitors and cardiac neural crest cells, leading to heart tube elongation and arterial pole alignment defects and ultimately resulting in congenital heart defects including overriding aorta and ventricular septal defects.

Resident Cardiac Stem Cells and Cardiac Repair

The newly identified second heart field population, giving rise to a large part of the heart, has been recently described to be the source of resident cardiac stem cells in the mammalian heart. Indeed, undifferentiated cardiac progenitors have been identified in fetal and postnatal myocardium that specifically expressIsl1, a transcriptional regulator of the SHF, and have the potential to fully differentiate into a cardiomyocyte phenotype. Heart disease is the number one killer in adults and the major non-infectious cause of death in children. Indeed, congenital heart defects, the most common congenital malformations in newborns, are present in almost one percent of live births, and acquired heart diseases, such as heart failure, represent one of the leading causes of death and hospitalization. SHF-derived cardiac resident stem cells thus identify a

Francesca Rochais (Marseille, France) was the winner of the ISHR-ES/SERVIER Research Fellowship 2008 at the XXVIII European Section Meeting (Athens, Greece; June 2008).
candidate cell population for potential cell therapy to repair damaged myocardium. Understanding the signals that control development of the SHF in the early embryo can provide insights into the mechanisms that maintain and direct the differentiation of cardiac progenitor cells in the later heart. Our results implicating Hes1 in SHF development are thus potentially clinically relevant for cardiac repair in the context of both congenital and acquired heart disease.

References


4. Cai C et al. Isl1 identifies a cardiac progenitor population that proliferates prior to differentiation and contributes a majority of cells to the heart. Dev Cell 2003; 5: 877-889.

5. Xu H et al. Tbx1 has a dual role in the morphogenesis of the cardiac outflow tract. Development 2004; 131: 3217-3227.


8. Bajolle F et al. Myocardium at the base of the aorta and pulmonary trunk is prefigured in the outflow tract of the heart and in subdomains of the second heart field. Dev Biol 2008; 313: 25-34.


Francesca Rochais, PhD
Marseille, France
HEART NEWS AND VIEWS

is published thanks to an unrestricted grant from Servier

a private French pharmaceutical company committed to therapeutic advances in cardiovascular medicine as well as other key therapeutic areas. We have successfully developed products in the field of cardiovascular diseases (ischemic heart disease, hypertension, and heart failure), as well as in other major therapeutic fields. A number of landmark studies like PROGRESS, EUROPA, PREAMI, ADVANCE, HYVET, and BEAUTIFUL are, or have been, conducted with our support.

The dynamism of our research is ensured by consistent allocation of as much as over 25% of the annual turnover of the Group to search for new molecules and develop their therapeutic applications.

Servier is also the founding father of The European Cardiologist Journal by Fax and Dialogues in Cardiovascular Medicine, a quarterly publication with a worldwide circulation edited by Roberto Ferrari and David J. Hearse. Dialogues discusses in a comprehensive way issues from the cutting edge of basic research and clinical cardiology.

Visit the Web version at www.dialogues-cvm.org

The forthcoming issue, devoted to SURROGATE END POINTS IN HEART FAILURE TRIALS will feature articles by:

I. S. Anand and V. G. Florea;
T. A. McDonagh; T. F. Lüscher et al;
M. A. Pfeffer and H. Skali

For further information on Dialogues in Cardiovascular Medicine please contact:
Dr Irina Elyubueva - Servier International
35 rue de Verdun - 92284 Suresnes Cedex - France
or webmaster@servier.com

Heart News and Views
is the official News Bulletin of the International Society for Heart Research and is published every fourth month.

Editor
L. Anderson Lobaugh
Durham, NC, USA
E-mail llobaugh@nc.rr.com

Founding Editor
T.J.C. Ruigrok
Wijk bij Duurstede, The Netherlands
E-mail t.j.c.ruigrok@xs4all.nl

Editorial Board
R.A. Altschuld
Columbus, OH, USA
M. Avkiran
London, UK
President-Elect
R. Bolli
Louisville, KY, USA
Past-President
T. Izumi
Kanagawa, Japan
Japanese Section
H. Kiriazis
Melbourne, Australia
Australasian Section
X.Y. Li
Beijing, China
Chinese Section
A. Mattiazzi
La Plata, Argentina
Latin American Section
B. McDermott
Belfast, UK
European Section
E. Murphy
Bethesda, MD, USA
North American Section
T. Ravingerova
Bratislava, Slovak Republic
N. Takeda
Tokyo, Japan
K.K. Talwar
Chandigarh, India
Indian Section
D. Eisner
Manchester, UK
Editor-in-Chief, JMCC
B.J. Ward
London, UK
K.T. Weber
Memphis, TN, USA

Editorial Office
3711 Lochn’ora Parkway
Durham, NC 27705
USA.
Phone/Fax: +1 919 493 4418