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THE HEART OF HAIFA



The XXX Annual Meeting of the European Section (2011) was held in the beautiful city of Haifa, Israel. Over 150 abstracts and 70 oral presentations were chosen by the organizing committee to give profound insight into the state of the art of cardiac science. The meeting covered the hottest topics of the day: cardiac stem cells and regeneration, the role of mitochondria and the nucleus in cardiac pathophysiology, extracellular matrix and fibroblasts, epigenetics and microRNAs, heart failure and remodeling, ischemia/reperfusion and cardioprotection, and many more. A combination of organized debates and spontaneous discussions made the meeting spectacular and engaging, allowing very few to doze off in the lecture hall.

The meeting opened with a brief get-together in the Tikotin Japanese Art Museum. Light but timely snacks in combination with excellent Israeli wine provided a fine atmosphere to meet old friends and newcomers. Perhaps the majority of attendants were



Attentive delegates listen to the opening lecture at the Ruth and Bruce Rapaport Faculty of Medicine, Technion, Israel Institute of Technology.

acquainted from previous ISHR meetings; however, a lot of delegates were attending for the first time. A cozy inner courtyard was an ideal place for greetings and quiet informal conversation.

The next morning, buses drove the participants over to the conference site in the Faculty of Medicine of the Technion, the Israeli Institute of Technology, soon to be 100 years old. The tall white building of modern architecture rises at the waterfront, cooled by the Mediterranean breeze. Standing on the cutting edge of Israeli science, the entrance to the faculty of



The poster sessions were well-attended and encouraged lively discussion.

medicine and the adjacent medical center is guarded by uniformed guards and metal detectors (like most Israeli public institutions).

A quick ceremony was followed by the opening lecture on mechanisms of myocardial hibernation by Eli Keshet (Hebrew Univ). The lecture outlined a role of VEGF in myocardial remodeling analyzed using elegant transgenic mouse models. After a brief coffee break, the first

men Meitner (Univ of Cambridge) - were of extraordinary scientific quality. The winning presentation by Marc Hirt (Univ Med Ctr Hamburg-Eppendorf) reflected a true miracle of how tissue engineering can be used to study the physiology of the heart. The model in which cardiac myocytes are grown on a scaffold and deliver real-life contractile performance is a novel approach and the result of outstanding laboratory work. The first prize, in my opinion, was very well deserved (sighing).

Day two began with several exciting and scientifically novel symposia. Stem cells are never going out of fashion, as demonstrated by a number of excellent

Tom Eschenhagen (ES President), Sian Harding (ES Past-President), Moshe Flugelman (meeting secretary, Haifa, Israel) and Denis Loiselle (New Zealand) stand in front of the winning posters.



sessions gave a fresh look at the ever-important cardiac problems: developmental issues, calcium metabolism, arrhythmias and myofilament function, cardiac implications of exercise and cancer, and also common aspects of atrophy and hypertrophy. They were succeeded by the Young Investigator Award competition, where I was honored to be one of the five finalists. The lectures delivered by my competitors - Dusan Bilbija (Oslo Inst of Basic Med Sciences), Shimrit Lieber (Tel Aviv Univ), and Car-

invited speakers. The parallel symposia also showed that cardiac researchers are looking for clues "outside the box". The role of fibroblasts, AMPK and thyroid hormones was examined, and a clear highlight of the day was a session on microRNAs - recently discovered pieces of cellular machinery that fine-tune protein synthesis and operate in a new and mysterious way. The presenters showed a pivotal role of MiR-21 in heart failure, and MiR-24 in angiogenesis. The session culminated in a lecture by Mordechai Choder (Israel Institute of Technology) that introduced the concept of Synthegradosome. The lecture had broad scientific appeal, and left the audience with a new understanding of mechanisms regulating translation of RNA.



Meeting delegates visit the beautiful archaeological site in Tzipori.



Delegates relax on the dance floor following the meeting dinner.

Finally, two consequential debates were held in the last session of the day, which explored long-standing controversies in two major areas of research. A clash of concepts to explain the protective effect of postconditioning was presented by Gerd Heusch (Univ of Essen Med Sch) and Derek Yellon (Univ College London). Both speakers presented abundant evidence for their theories, and the arguments fell just short of the vibrancy and liveliness of the American presidential debates. Next, Martin Bergmann (Asklepios Klinik St. Georg) and Loren Field (Wells Center/Riley Hosp) argued *pro et contra* the existence of myocyte resident stem cells. The popular vote revealed that the majority of delegates were rather skeptical.

When the lectures were over, the participants were driven to the beautiful archeological site in Tzipori. A walk among the ruins and the biblical landscapes was refreshing and educational, while the tour guides did a terrific job. The Israeli weather gave us a real treat, hiding the sun in a gentle haze. After the walk, the crowd was brought to an Arabic restaurant, looking rather like a palace in the middle of the desert. A bus ride in the dark left us clueless as to where the restaurant was

located. The cultural impact of the dinner was nearly as strong as the gastronomical impact. The Arab dancers were flying between the tables, encouraging the guests to dance along. The food was abundant and delicious.

Among the highlights of the last day were Fabio Di Lisa's (Univ of Padua) lecture on mitochondrial stress, and Marte Blikspen's (Oslo Univ Hosp Ullevål) talk on mitoDNA. The latter had never been brought into focus before, and attracted significant attention from the audience. David Garcia-Dorado (Hosp Univ Vall Hebron) delivered an in-depth presentation of the role of cGMP in postconditioning, and an entire symposium was dedicated to a discussion of the role of extracellular matrix in the mechanisms of myocardial remodeling and repair. The parallel sessions on epigenetics and regulation of contractility were also said to be excellent.

The last session was dedicated to award presentations and special lectures. The 2010 ISHR-ES/SERVIER award winner, Atsuko Kasahara, discussed her work on "Exploring the role of mitochondria-shaping protein in cardiomyocyte differentiation of mouse embryonic stem cells". The 2011

ISHR-ES/SERVIER Research Fellowship winner was Marie Schroeder (Univ of Oxford). In a lecture that exemplified outstanding scientific work, the President's Distinguished lecturer, Sian Harding (Nat'l Heart & Lung Inst) described a rare cardiac pathology (Takotsubo Cardiomyopathy) that provides a key to understanding the effect of excessive adrenergic stimulation on human cardiac function, and has direct clinical implications for the treatment of patients following significant psycho-emotional stress.

Many guests chose to spend a few extra days in Israel after the meeting was over. This was not unexpected, given the fantastic weather, warm water almost devoid of jellyfish, and tremendous hospitality that we enjoyed everywhere in the country. We appreciate the hard work of the meeting organizers, which resulted in a delightful scientific, cultural and personal experience.

Arkady Rutkovskiy ■

This meeting was supported by generous donations from the Technion, IIT, the Dahlia Greidinger Fund, Haifa, and the City of Haifa.

PRESIDENT'S LETTER



Thanks for the donation from the ISHR for the triple disasters in Japan.

On March 11, Japan was struck by a magnitude 9.0 earthquake off the northeast Pacific coast of the Tohoku region. The quake generated a devastating tsunami with waves estimated to reach 38 m. As a result of the main quake and ensuing tsunami, reactors within the Fukushima No.1 nuclear plant were severely damaged with consequent radiation leaks. As of July, the number of confirmed dead was 15,601, and 4,968 people were missing or unaccounted for (down from 9,600 reported at the end of May). 75,000 people displaced by the disaster remain in evacuation centers and other temporary housing within the three most affected prefectures.

Immediately after the quake, Japan DMAT (Disaster Management Assistance Team) dispatched a total of 365 teams to the stricken areas, providing a total of 1600 medical personnel during the first few days. To our regret, however, many people were trapped in houses destroyed by the tsunami, and DMAT was unable to save many of the the injured people. Since the affected Tohoku region faced a serious shortage of physicians even before it was hit by the calamity, many DMAT teams prolonged their service to support the health care systems at the local hospitals. To provide medical services during the acute phase, the Japan Red Cross Society dispatched 733 teams and the Japan Medical Association (JMA) provided 940 medical teams during the first three months. Our medical center in Osaka also dispatched three medical teams with physicians, nurses, pharmacists and clerks to the mostly damaged area in the Tohoku region to support the health care service at the evacuation center and at mobile clinics in the community.

During the first week after the quake, more than one thousand patients treated with chronic hemodialysis at severely damaged hospitals (with water/power supplies lost) were transferred to other hospitals in this remote area. Less damaged hospitals in the stricken area provided ambulatory hemodialysis at 24 hours. Oxygen gas cylinder suppliers provided emergency supplies to registered patients with home oxygen therapy (HOT) at evacuation centers or at their homes. The suppliers also set up several oxygen gas supply centers in the middle of the affected region. For patients with diabetes mellitus treated with insulin, JMA and the Japan Diabetes Society provided the quick delivery of insulin and syringes to maintain these patients' insulin treatment. Thirty tons of drugs for common diseases (*e.g.* headache, insomnia, gastroenteritis, influenza, hypertension and diabetes) were transported to the Tohoku area with the support of the US Army. Many warfarin tablets were also provided along with POC equipment, including coagulometers to check prothrombin time. In some areas, DVT (Deep Vein Thrombosis) teams checked for venous thrombosis in immobile elderly people who were staying at the evacuation centers. With a substantial supply of drugs and the extensive medical support of government and voluntary groups, health care services in the Tohoku area have now recovered fairly well. However, it is not yet clear whether the incidence of acute coronary syndrome, stroke and Takotsubo myopathy have been increased in the affected population as observed in previous disasters. Undoubtedly, there is a growing number of "invisible" deaths among evacuees who have died after developing an illness or seeing their pre-existing conditions worsen following the quake. It is reported that such invisible deaths doubled during the three months following the quake, and that most deaths occurred in elderly people. It is fortunate that the earthquake victims have not suffered from a pandemic of infectious diseases or from serious damage caused by PTSD (posttraumatic stress disorder).

In this disaster, the nuclear crisis precipitated by the Fukushima No.1 power plant's accident spread the damage to a larger geographical area. Immediately after the nuclear leak, the government created a 20 km exclusion zone around the plant from which the residents were evacuated. Accordingly, some 80,000 people were forced from their homes, leaving towns almost completely empty. Growing concern over the safety around the nuclear plant caused an economic decline due to rumors that the farm products and fish/meat from Fukushima had been adversely affected by the radiation leak. It should

REPORT ON THE XXXII MEETING OF THE NORTH AMERICAN SECTION (MAY 2011)

PHILADELPHIA: HEART FAILURE IN THE CITY OF BROTHERLY LOVE

The 32nd annual meeting of the International Society for Heart Research, North American Section, was held this May in Philadelphia, Pennsylvania at the Doubletree Hotel. The focus of this year's meeting was "Developing Novel Heart Failure Therapeutics." The city of Brotherly Love is perhaps best known as the birthplace of the American Revolution. The site of the signing of both the Declaration of Independence and the US Constitution, Philadelphia served as the temporary capital of the United States prior to 1800 while Washington DC was under construction. No trip to Philadelphia is complete without visits to our most historic landmarks: the Liberty Bell at Independence Hall, Reading Terminal Market, the Philadelphia Museum of Art (where Rocky ran up the stairs), and Pat's and Geno's (South Philly's legendary cheesesteak restaurants). The prevalence of fatty foods and a concentration of medical research institutions make Philadelphia the ideal location for this year's meeting on novel heart failure therapeutics. The first hospital in the United States, Pennsylvania Hospital, still operates in Center City, and Philly is home to 5 medical colleges (one osteopathic), the American College of Physicians and many more academic and private research institutions.

The conference began on Sunday with Interest Group workshops on cardiac signaling pathways, heart failure, arrhythmias, contractile proteins, E-C coupling, and metabolism, and the day culminated with the Young Investigator Award competition. Four junior candidates (graduate students or post-doctoral fellows

within 4 years of completing their degrees) and three senior candidates (senior postdoctoral fellows or early assistant professors) were chosen as finalists based on evaluation of an unpublished manuscript by the YIA committees (chaired by Drs Litsa Kranias (Junior YIA Committee) and Paul Simpson (Senior YIA Committee)).

After oral presentations of their research, one winner was selected from each group of Finalists to receive the ISHR 2011 Young Investigator Award (YIA). This year's Junior YIA Finalists included Mark Kohr (JHMI), Tiffany Nguyen (NIH/NHLBI), Laetitia Pereira (UC-Davis), and Domenico Taglieri (University of Illinois-Chicago). The Junior YIA was awarded to Mark Kohr, mentored by Dr Charles Steenbergen, for his project "Redox modifications play a critical role in myocardial ischemic precondition." The Senior YIA Finalists included Shinichi Oka (UMDNJ), Sanjeeva Goonasekera (Cincinnati Children's Hospital Medical Center), and Jeffrey Erickson (UC-Davis). The Senior YIA was awarded to Jeffrey Erickson, mentored by Dr Donald Bers, for his project "The novel FRET sensor Camui provides new insight into mechanisms of CaMKII activation in cardiomyocytes."

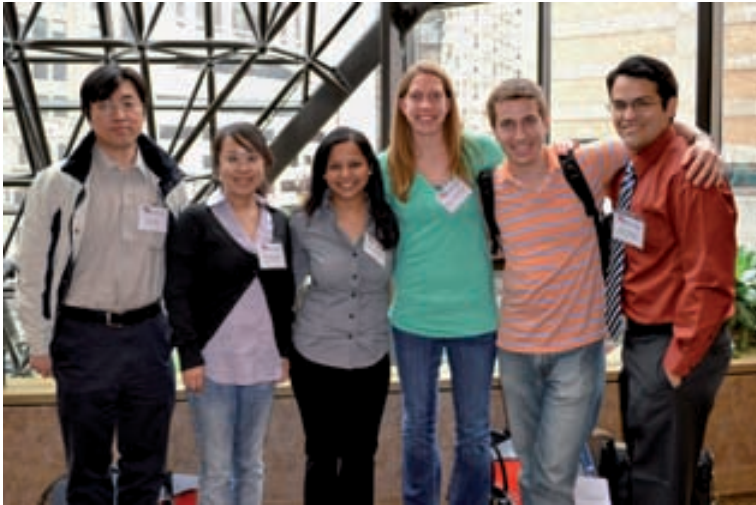
Following the Young Investigator competition was the opening reception in the Symphony Ballroom. Investigators gathered from across the United States, from Canada and from as far away as the United Kingdom, Brazil, Argentina and Australia, to celebrate the opening night of the conference and to honor the 60th birthday of this year's conference co-organizer, Dr Steven Houser of Temple University School of Medicine. The evening was festive, and cake was enjoyed by all.

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be noted, however, that low dose radiation exerts an effect similar to oxidative stress: the generation of ROS. There are a number of experimental reports which demonstrate that a low dose (<500mSV) of radiation can exert a protective effect as in "ischemic preconditioning" and can even prolong the life span. Although too much concern over the nuclear hazard may misdirect the world's future energy policy, there should be a heated discussion to evaluate the pros and cons of nuclear power. Twenty-nine of the 54 nuclear plants in Japan are now out of service and their recovery is not promising.

In this disaster, Japan has lost more than 20,000 lives and 2,000 billion dollars. We have to rise to the task of reconstruction and support the affected people for a long time. On behalf of the ISHR members of the Japanese Section, I heartily thank you for the donation of \$7,600 from the ISHR to the Japan Red Cross. It will greatly contribute to the recovery of the people in the affected area.

*Masatsugu Hori, M.D., Ph.D.
President ISHR*



Members of the Houser Lab (Temple University School of Medicine, Center for Cardiovascular Research) arrive at the Doubletree Hotel for the conference (from left): Dr Hui Gao (Post-doctoral fellow), Fang Wang (4th Year PhD candidate), Foram Udeshi (Masters Student), Cat Makarewich (3rd Year PhD candidate and co-author), Jason Duran (4th Year MD/PhD Candidate and co-author), Larry Barr (4th Year PhD candidate).



Visitors making new friends at the reception (from left): Alastir Kerr (GlaxoSmithKline), Christian James (GlaxoSmithKline), Rong-lih Liao (Harvard), Rong Tian (University of Washington), Ying Ge (University of Wisconsin), Pei Pei Ping (UCLA), and Doug Lewandowski (University of Illinois-Chicago).

Monday featured two rounds of lively symposia with a morning plenary lecture by Dr Howard Rockman (Duke Univ Medical Center) and an afternoon featured talk by Dr James M. Wilson (Univ of Pennsylvania). The day began with Dr Rockman, who offered his perspective on “Novel approaches to identify and test heart failure therapies.” The two morning sessions focused on “Novel signaling pathways that induce pathological hypertrophy”, mod-

erated by Dr Abdelkarim Sabri (Temple Univ), and “Metabolic defects in the failing heart”, moderated by Dr Gary Lopaschuk (University of Alberta). A special afternoon seminar was given by Dr Wilson, who discussed the applications for novel gene therapy, specifically the use of tissue-targeted adeno-associated viral vectors, in the treatment of cardiovascular disease. The two afternoon sessions focused on “Model organisms for heart failure discovery”, moderated by Dr Ju Chen (UCSD), and “Omic solutions to heart failure”, moderated by Richard Kitsis (Albert Einstein). The day culminated in the first of two Poster Sessions, which featured 77 posters and was followed by the Faculty dinner.

Tuesday also featured two rounds of parallel symposia and two plenary talks. Dr Roger Hajjar of Mount Sinai Medical Center, began the day with his discussion on “Translating heart failure targets into therapy.” The morning session featured discussions on “Heart failure insights from developmental

biology”, moderated by Dr Natalia Riobo (Thomas Jefferson University) and “Defective Ca²⁺ handling in the failing heart”, moderated by Dr Xiongwen Chen (Temple University). The afternoon plenary talk was given by Dr David Kass from Johns Hopkins Medical Institute and focused on “Novel therapies to reverse structural and functional defects in the failing heart.” The afternoon session featured a spirited discussion on “Recent advances in cell-based therapies for heart failure”, moderated by our conference co-organizer, Dr Steven Houser, and “Signaling between sarcomeric proteins and cardiac ion channels” moderated by Dr Mark Ziolo of Ohio State University. At the end of the day on Tuesday, the 2011 ISHR Outstanding Investigator Award was presented to Dr Walter J. Koch, the other co-organizer of this year’s meeting and professor at Thomas Jefferson University. Dr Koch delivered his honorary award lecture entitled “Is it translation or perseverance? GRK2 and S100A1 as targets for heart failure gene therapy.”

Following Dr Koch’s award ceremony was the second Poster Session, featuring 74



At the opening reception, meeting co-organizer Steve Houser blows out the birthday candles on a giant birthday cake to celebrate his 60th birthday.

new posters; the combined poster sessions from Monday and Tuesday featured the work of over 600 investigators. After the second poster session was the annual ISHR Conference Banquet. At this dinner, the Junior and Senior YIA's were announced, and ISHR-Intl Poster Awards were given to several additional young investigators for their outstanding posters. Poster award winners included: Drs Chia-Wei Chang (UC-Davis), Anna Gumpert (Thomas Jefferson), Sun Haipeng (UCLA), Marcus Henze (UIC),

Jop Van Berlo (CCHMC), and Yaniv Yael (NIH/NIA). The evening culminated with a night of dancing, and featured dazzling karaoke performances from our conference co-organizers, Drs Steven Houser and Walter Koch, whose renditions of Rihanna's "S&M" and Lady Gaga's "Poker Face", respectively, will never be forgotten.

The conference concluded on Wednesday with closing remarks from our hosts, Drs Houser and Koch, followed by the 2011

Keith Reimer Distinguished Lecture by Dr Charles Murry (Univ of Washington). Dr Murry, a former graduate student in Dr Reimer's laboratory at Duke Univ Medical Center, gave his lecture on "Regenerating the heart: A case for rational optimism" and discussed memories of his former mentor, who passed away in 2002. The conference then concluded with two morning sessions on "Ion channels and arrhythmias in heart failure", moderated by Dr Joseph Cheung (Thomas Jefferson University) and "Car-



Junior Young Investigator Finalists (from left): Mark Kohr (Winner, Johns Hopkins, Mentor: Charles Steenbergen), Tiffany Nguyen (NIH/NHLBI, Mentor: Elizabeth Murphy), Domenico Taglieri (University of Illinois-Chicago, Mentor: John Solaro), and Laetitia Pereira (UC Davis, Mentor: Don Bers), and Senior Young Investigator Finalists: Jeff Erickson (Winner, UC-Davis, Mentor: Don Bers), Sanjeewa Goonasekera (Cincinnati Children's Hospital, Mentor: Jeff Molkentin), and Shinichi Oka (UMDNJ, Mentor: Jun Sadoshima).



Winners of the ISHR Intl Poster Competition (front row, beginning second from left): Anna Gumpert (Thomas Jefferson Univ), Chia-Wei Chang (UCSD), Jop Van Berlo (CCHMI), Yael Yaniv (NIA, NIH) and Hai-peng Sun (UCLA). Winner Mark Henze (UIC) was not in attendance. Guo-chang Fan (Univ of Cinn; front row, far left) is also pictured. Second row: Donald Bers (President, ISHR-NAS) and Mark Sussman (ISHR-Intl Council member and organizer of the poster judging).



Meeting co-organizer Wally Koch and the Manchester contingent. From left: Jessica Clarke, Sarah Briston and Margaux Horn (Univ of Manchester).

dioprotection for the failing heart", moderated by Dr Art Feldman (Thomas Jefferson University). Overall, the meeting was stimulating and productive, new collaborations were fostered, and many researchers were inspired to advance the future of heart failure therapeutics.

Jason Duran and Cat Makarewich ■

Both authors contributed equally to this article.

MATHIAS GAUTEL, M.D., PH.D.

WINNER OF THE 2009 OUTSTANDING INVESTIGATOR AWARD

(MAY 2009; NICE, FRANCE)



MG
MATHIAS GAUTEL was born in 1963 in Karlsruhe, Badenia (Germany) where he grew up. He studied Medicine at Heidelberg University, Germany, graduating in 1991 with an MD “*summa cum laude*”. During his medical studies, he commenced research on the giant muscle protein titin, for which he obtained the first cDNA clones in 1988. He subsequently continued to pursue research on titin at the European Molecular Biology Laboratory in Heidelberg, first as a Postdoctoral Fellow of the German Research Foundation (DFG) and then as an independent team leader with a Habilitation Fellowship of the DFG in the Structural Biology Division. Dr Gautel obtained his Habilitation (MD PhD equivalent) in Biochemistry from the Medical Faculty of Heidelberg University in 1996. In 1998, he was awarded a Heisenberg Fellowship, the highest award of the DFG for young independent scientists, to work at the Max-Planck Institute of Molecular Physiology in Dortmund. Since 2002, he has been Professor of Molecular Cardiology at King’s College London, where he was awarded a British Heart Foundation Chair in 2008.

Dr Gautel’s research centres on the analysis of striated muscle proteins involved in cytoskeletal assembly and signalling, and their involvement in heart disease. His contributions towards elucidating the basic molecular architecture of the giant protein titin, its interactions with other sarcomeric proteins (several of which he has discovered), and their regulation, atomic structure and biomechanics, have significantly furthered our understanding of

the involvement of the titin protein network in human muscle diseases. Dr Gautel’s work has made seminal contributions to the understanding of the protein interactions of titin in the sarcomeric Z-disk, A-band and M-band, with his discovery of length-adjusting elements in Z-disk titin and new proteins interacting with Z-disk and M-band titin allowing reconstructions of the molecular layout of these structures. The discovery of the giant protein obscurin in his laboratory has led to a new paradigm in muscle cell biology and has opened up the novel field of proteins with multiple sarcomeric localisation at Z-disks and M-bands. The crucial role of obscurin in M-band assembly was underscored recently by his discovery of a ternary complex of titin, obscurin and the M-band protein myomesin; this complex is disrupted in two different hereditary myopathies with mutations in titin. Dr Gautel’s pioneering contributions to titin single molecule analysis unravelled the molecular mechanism of muscle passive elasticity, and recently, of the mechanoenzymatics of the titin kinase domain. Through a long-standing structural, biochemical and cell biological effort devoted to the signalling functions of the protein kinase domain of titin, his work has led to the novel concept of a mechano-regulated protein kinase that is implicated in load dependent protein turnover in muscle. He has identified a new signalling pathway emanating from the titin kinase domain, and shown that this is disrupted in a hereditary myopathy with titin mutation. His recent work has revealed, for the first time, how a protein kinase can be activated by mechanical strain. This new paradigm of kinase mechanosignalling

may be relevant to a large number of cytoskeletal protein kinases that have been implicated in cardiovascular regulation.

Dr Gautel’s identification and analysis of the primary sequence of cardiac myosin-binding protein-C (cMyBP-C) has led to the discovery that this gene was responsible for chromosome 11-linked hypertrophic cardiomyopathy, now realized to be the most commonly affected gene in this disease. Investigations in his laboratory have revealed how cMyBP-C interacts with titin and myosin, and how phosphorylation of a specific domain contributes to the regulation of cardiac contraction. Dr Gautel was the first to identify and characterize the phosphorylation of cMyBP-C at the molecular level, to delineate its structural and regulatory interactions, and to realize its involvement in familial hypertrophic cardiomyopathy.

Dr Gautel has published numerous papers in the foremost biomedical journals, and through implementation of his basic research findings, has been able to elucidate the molecular mechanism of disease-associated mutations in myosin, myosin-binding proteins and titin. His work has combined, in a rare manner, cellular, molecular and structural approaches with a profound interest in disease mechanisms. The pioneering work of Dr Gautel in muscle research and his continued scholarly contributions are also reflected by his long-standing service on the funding committees of international agencies in France and the United Kingdom. He is associate editor of the *Journal of Muscle Research and Cell Motility*. ■

THE KEITH REIMER
DISTINGUISHED LECTURE 2011

REGENERATING THE HEART:
A CASE FOR RATIONAL OPTIMISM

DR CHARLES MURRY

(MAY 2011; PHILADELPHIA, PA)



Dr CHARLES MURRY is a professor of Pathology, Bioengineering and Medicine/ Cardiology at the University of Washington in Seattle, where he also serves as the Director of the Center for Cardiovascular Biology and Co-Director of the Institute for Stem Cell and Regenerative Medicine. He received his BS in Chemistry from the University of North Dakota in 1982, after which he enrolled in the MD-PhD program at Duke University. His PhD research was done in the laboratories of Keith Reimer and Robert Jennings, studying mechanisms of cell injury during myocardial ischemia-reperfusion. This work included the first description of the phenomenon of ischemic preconditioning. In 1989 he graduated from Duke and entered residency training in Pathology at the University of Washington, followed by postdoctoral training in vascular biology with Stephen Schwartz. He was appointed as an assistant professor of Pathology in 1996 and as professor in 2004. Murry's awards include the Burroughs Wellcome Career Award in Biomedical Sciences, the AHA's Council on Basic Cardiovascular Sciences Research Prize, the Presidential Early Career Award in Biomedical Sciences, and the University of Washington's Basic Science Teacher of the Year award.

Dr Murry currently serves on the editorial boards of *Circulation*, *Circulation Research*, and the *Journal of Molecular*

and Cellular Cardiology. He has served as a member of numerous study sections at NIH and as chair of the AHA's Pathophysiology study section. He has served as a Councilor and Scientific Program Director for the Society for Cardiovascular Pathology, and he is currently a Councilor for the ISHR and chairs its Stem Cell and Gene Therapy Interest Group. Murry has served as an organizer for multiple international conferences including the Heart Failure Society of America scientific sessions, the CRT Angiomyogenesis and Cell Therapy Conference, the NHLBI Symposium on Cardiovascular Regenerative Medicine, the Keystone Symposium on Cardiovascular Death, Growth and Regeneration, and he is serving as co-chair of the upcoming SBE/ISSCR International Conference on Stem Cell Engineering.

Dr Murry's current research is directed at understanding molecular pathways regulating cardiovascular differentiation from pluripotent stem cells, and then using these cells to promote remuscularization and revascularization of the injured heart. He has authored over 100 peer-reviewed papers and has supervised more than 20 undergraduates, 15 graduate students, and 23 postdoctoral fellows, many of whom have gone on to leadership positions in academia and industry. His research program is multidisciplinary, spanning cell biology, integrative physiology, bio-

engineering and clinical studies. His group pioneered the use of gene therapy and cell transplantation to promote growth of new muscle in the infarcted heart and established protocols for directing the differentiation of human pluripotent stem cells into cardiomyocytes. They showed that transplanting human cardiomyocytes or engineered human heart tissue forms human myocardium in experimentally infarcted hearts, thereby preventing development of heart failure. Most recently, Dr Murry's focus has turned to the derivation of induced pluripotent stem cells from patients with genetically based cardiomyopathy. They are establishing systems for understanding genotype-phenotype correlations in cardiomyopathy, with a long term goal of identifying novel therapies for these diseases. ■

DR WALTER J. KOCH

IS IT TRANSLATION OR PERSEVERANCE? GRK2 AND S100A1 AS TARGETS FOR HEART FAILURE GENE THERAPY

WINNER OF THE 2011 OUTSTANDING INVESTIGATOR AWARD

(MAY 2011; PHILADELPHIA, PA)



Dr WALTER J. KOCH is the W. W. Smith Professor of Medicine and currently serves as Director of the Center for Translational Medicine and Vice Chair for Research in Department of Medicine at Thomas Jefferson University. Dr Koch received his Ph.D. in Pharmacology and Cell Biophysics in 1990 in the laboratory of Dr Arnold Schwartz at the University of Cincinnati. Following this he began a Howard Hughes Post-Doctoral Fellowship in the Laboratory of Dr Robert J. Lefkowitz at Duke University Medical Center. In 1995 he was recruited to start a molecular cardiovascular biology laboratory in the Department of Surgery at Duke. While a faculty member at Duke, Dr Koch rose quickly and became a tenured Full Professor of Surgery within 6 years of starting his independent laboratory. Dr Koch moved to Jefferson in 2003 to build the Center for Translational Medicine where he has recruited 12 primary tenure-track faculty. These Center faculty members under Dr Koch's leadership carry out basic and translational studies in cardiovascular disease.

Dr Koch has received numerous honors and awards prior to being named the 2011 Outstanding Investigator of the International Society for Heart Research including presenting the Thomas Smith Memorial Lecture at the 2009 American Heart Association Meetings. Dr Koch was presented with the Davison Award for

Teaching while at Duke and won the Jefferson Medical College Inaugural Career Achievement Award in Biomedical Sciences in 2010. He has also been named a Fellow of the AHA and last year was named a Fellow of the ISHR. Dr Koch is currently well funded through the NIH and holds a MERIT Award from the NHLBI and is the Principal Investigator of a Program Project Grant. He also is a named inventor of 8 patents.

In 2010, Dr Koch ended his tenure as Chair of the CCHF NIH study section and reviews grants for several international committees. He currently is a member of the Recombinant DNA Advisory Committee (RAC) of the NIH. He is an Associate Editor of *Circulation Research* and an Executive Editor of *Clinical and Translational Science*. He is also currently the Co-Chair of the Basic Cardiovascular Science (BCVS) Council of the American Heart Association.

Specifically in the Koch Laboratory, studies are focused on the adrenergic receptor system in heart failure. Over the last two decades the Koch lab has focused on the role of G protein-coupled receptor (GPCR) kinases (GRKs) and the role they play in normal and failing heart function including how they regulate adrenergic receptors. They have found that one GRK, GRK2, is pathological in the heart both acutely and chronically after myocardial stress/injury.

More recently, they have uncovered novel roles for GRKs in the heart independent from their receptor kinase functions. Overall, Dr Koch has published over 250 peer-reviewed articles that has led to over 12,000 citations. This includes 36 articles cited over 100 times and he currently has an h index of 57 (57 papers references at least 57 times).

While a post-doctoral fellow, Dr Koch showed in a paper published in *Science* in 1995 that manipulation of GRK2 activity in the heart could have profound effects on *in vivo* cardiac function. Dr Koch developed and discovered a peptide inhibitor of GRK2, named the β ARKct, which has led to the elucidation of several important aspects of GRK2 in the heart including it being pathological following cardiac injury. Subsequently, working collaboratively with Dr Howard Rockman, Dr Koch went on to show that inhibition of GRK2 in the heart could rescue several mouse models of heart failure. Dr Koch's work also heavily involved cardiac gene therapy research where his team at Duke developed novel models of coronary artery delivery of viruses carrying potentially therapeutic transgenes. In 2009, Dr Koch published a landmark paper showing that chronic inhibition of cardiac GRK2 using β ARKct delivered via an adeno-associated viral (AAV) vector could rescue a heart failure model in the rat.

(continued on page 15)

THE PRESIDENT'S LECTURE 2009

INTEGRATION OF CARDIAC SARCOMERIC CONTROL MECHANISMS WITH EC COUPLING AND METABOLISM

R. JOHN SOLARO, PH.D.
(MAY 2009; BALTIMORE, MD)



Dr SOLARO is Head of the Department of Physiology and Biophysics in the College of Medicine at the University of Illinois at Chicago, and Distinguished University Professor at the University of Illinois. He is also past Director of the UIC Center for Cardiovascular Research. At UIC, Dr Solaro has received the University Scholar Award, the Faculty of the Year Award, and the Mentor of the Year Award. Dr Solaro is currently Chair of the Skeletal Muscle and Exercise Physiology Study Section. He serves as Associate Editor of the *Journal of Molecular and Cellular Cardiology*

and is past Associate Editor of the *American Journal of Physiology (Heart)*. He also serves on the editorial board of *Circulation Research*.

Dr Solaro's major research interest is in the general area of cellular and molecular mechanisms controlling the contraction and relaxation of the heart, how these mechanisms are altered in pathological conditions, and how they are modified by pharmacological interventions. The focus is on the integration of signaling and signal transduction at the level of the cardiac sarcomere. He has done seminal work on

the role of troponin in switching on contraction, on the role of myofilament protein phosphorylation in the control of cardiac dynamics and in the transition to heart failure, and on the enhancement of myofilament activation by pharmacological agents, two of which Acardi (Pimobendan) and Simdax (Levosimendan) are in clinical use. His current studies focus on multiplex functions of sarcomeric proteins and the Z-disc protein network in contraction/relaxation and signaling. ■



THE PRESIDENT'S LECTURE 2010

A NOVEL MOLECULAR MECHANISM AND REGENERATION THERAPY FOR HEART FAILURE

ISSEI KOMURO, M.D., PH.D.
(MAY 2010; KYOTO, JAPAN)

Dr KOMURO is professor and chairman of cardiovascular medicine at Osaka University, where there are many severe heart failure patients, and his interest is now how to establish novel treatments for heart failure.

Dr Komuro is a pioneer in, and has made great contributions to, the research fields of cardiac hypertrophy and development.

His work has provided valuable insights into the pathophysiology of cardiac diseases; for example, elucidation of the molecular mechanism of mechanical stress-induced cardiac hypertrophy and heart failure. In the future, insights gained from the study of cardiac development will prove to be even more important to the burgeoning fields of gene therapy and regenerative medicine. Originality is a feature of Dr Komuro's research and he is also a highly

productive man. He has published over 450 original articles, many of which have appeared in leading journals including *Nature* and *Nature Medicine*. He has also published 50 book chapters/review articles, is a regular speaker at national and international meetings, and serves as an associated editor of *Circulation Research* and an editorial board member of *Journal of Clinical Investigation* and *Journal of Molecular and Cellular Cardiology*. ■

THE PRESIDENT'S LECTURE 2011

TAKOTSUBO CARDIOMYOPATHY –
LESSONS FROM A NATURAL PROTECTIVE
MECHANISM?

HONORED SPEAKER:
DR SIAN HARDING

(JUNE 2011; HAIFA, ISRAEL)



Prof HARDING's interests have centred on the function of the cardiac myocyte from the failing human heart since 1987, when she developed a method for the reliable isolation of intact myocytes from human atria and ventricles and established the suitability of the myocyte preparation (both human and animal) for constructing concentration-response curves to pharmacological agents.

Since that time, she has defined the main contractile deficits in myocytes from failing human heart, showing that the frequency response is lost and that stimulation through the betaAR is depressed through Gi-dependent mechanisms. Prof Harding was among those providing evidence for a role of SERCA2a loss and Gi up-regulation in these phenomena. Studies on animal models of betaAR desensitisation or overexpression, hypertrophy and heart failure, as well as adenoviral/AAV transfection of animal myocytes *in vitro* and *in vivo*, have unravelled processes underlying the alterations seen in human cells.

With Dr Roger Hajjar and Federica del Monte (a former Ph.D. student) at Harvard Medical School, she collaborated in the first studies to increase SERCA2a activity in myocytes from failing human heart, by adenoviral transfection of either SERCA2a itself, or antisense to the inhibitory protein, phospholamban. These studies estab-

lished that increase of SERCA2a activity was sufficient to restore contractile function in these cells. Further studies showed that this is not a pro-arrhythmic strategy either in human or animal myocytes, or in rat models of gene transfer. She is now part of the group developing a clinical trial for gene therapy in the UK, in parallel with an ongoing trial in the US, using AAV to transfer SERCA2a to failing human myocardium.

In search of a new model of the human ventricular myocyte, Prof Harding has built a group to study cardiomyocytes derived from human embryonic stem cells (hESC-CM) or induced pluripotent cells (iPSC-CM). She has adapted the methods used for adult myocytes, and has characterised their acute contractile and pharmacological phenotype as well as their response to hypertrophic and cardiotoxic agents. She is developing these cells, which can be maintained for months in culture and easily transfected, as an *in vitro* genotype-specific human cardiomyocyte model for high throughput investigations. She also has initiatives for stem cell implantation in combination with advanced materials.

A continuing interest in the betaAR system in failing human heart led to a major discovery concerning the mechanism of action of the beta-blockers; compounds which are standard therapy in heart failure. Prof Harding showed that these compounds

have effects over and above those related to catecholamine blockade, by activation of beta2AR-Gi coupling. Since the clinically-used beta-blockers differ in their ability to traffic the beta2AR through the protective Gi pathway, this finding will be highly relevant for the design and selection of compounds for future use in heart failure. Working with the advanced imaging techniques in Dr Julia Gorelik's laboratory, she recently published new insights into spatial modulation of betaAR signalling in myocytes and its disruption during the development of chronic heart failure.

Prof Harding's current interest is in the syndrome of Takotsubo or Stress Cardiomyopathy, in which acute severe heart failure follows a natural or iatrogenic adrenaline stimulus. The particular anatomical and epidemiological features of this, together with its relatively benign outcome compared to acute coronary syndromes, has led her to hypothesize an involvement of protective beta2-Gi coupling. She has developed *in vivo* and *in vitro* animal models to investigate this syndrome and draw parallels with the protective effects of beta-blockers in chronic heart failure. ■

Dr Harding is Professor of Cardiac Pharmacology at the National Heart and Lung Institute, Imperial College, London, and Past-President of the European Section of the ISHR.

MEET THE FUTURE OF THE ISHR-NORTH AMERICAN SECTION



Mark Kohr, Ph.D.: Winner of the 2011 ISHR-NAS Young Investigator Award (Graduate Students & Early Postdoctoral Fellows) XXXII North American Section Meeting (May 22-25, 2011); Philadelphia, PA
“Redox modifications play a critical role in myocardial ischemic precondition”

Dr Kohr is a NRSA fellow with a joint appointment in the laboratories of Dr Charles Steenbergen at Johns Hopkins University in Baltimore, MD and Dr Elizabeth Murphy at the National Heart Lung and Blood Institute in Bethesda, MD.

Dr Kohr’s major research interest centers on the role of protein S-nitrosylation and oxidation in cardioprotection

Jeffrey Erickson, Ph.D.: Winner of the 2011 ISHR-NAS Young Investigator Award (Senior Postdocs & Early Assistant Professors) XXXII North American Section Meeting (May 22-25, 2011); Philadelphia, PA
“The novel FRET sensor Camui provides new insight into mechanisms of CaMKII activation in cardiomyocytes”



Dr Erickson is currently an Assistant Researcher in the Department of Pharmacology at the University of California, Davis. His research focuses on the molecular pathways that underlie the transition to arrhythmia and heart failure, particularly as a result of oxidative stress and hyperglycemia. A key aim of his research is to describe the mechanisms that drive activation of CaMKII, a multi-functional kinase that plays a critical role in cardiac remodeling and dysfunction.

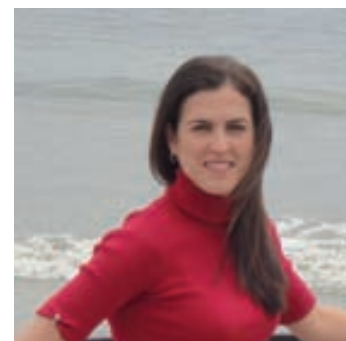


Grant R. Budas, Ph.D.: Winner of the 2009 ISHR-NAS Young Investigator Award (Graduate Students & Early Postdoctoral Fellows) XXXI North American Section Meeting (May 26-29, 2009); Baltimore, MD
“HSP90-mediated mitochondrial import of PKCε is essential for cytoprotection”

Dr Budas is a Research Scientist in the Cardiovascular Therapeutics department of Gilead Sciences, Palo Alto, California. His research aims to provide basic insight into cellular mechanisms underlying cardiac disease and to develop novel therapeutics. His major interest is in cell signaling, in particular the regulation and function of protein kinases during cardiac ischemia and heart failure.

Lina Shehadeh, Ph.D.: Winner of the 2009 ISHR-NAS Young Investigator Award (Senior Postdocs & Early Assistant Professors) XXXI North American Section Meeting (May 26-29, 2009); Baltimore, MD
“Regulation of compensatory angiogenesis during cardiac hypertrophy by a p300-miR-17-92 feedback loop”

Dr Shehadeh is an Assistant Professor in the Cardiovascular Division at the University of Miami Miller School of Medicine. Her major interest is elucidating mechanisms of microRNA regulation in vascular diseases, particularly the regulation and function of microRNA-gene networks in atherogenesis and stem cell differentiation.



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ISHR MEETINGS CALENDAR

- **October 7, 2011. XVIII Annual Meeting of the Latin American Section.** Buenos Aires (at the Favaloro Foundation), Argentina. **Organizers:** Drs Martin Vila Petroff (mvila@med.unlp.edu.ar), Alejandro Aiello and Margarita Salas
- **November 12-16, 2011. Scientific Sessions of the American Heart Association.** Orlando, Fl. *Website* www.scientificsessions.org
- **December 2, 2011. XXVIII Annual Meeting of the Japanese Section.** Tokyo (on Level 2, M&D Tower, Tokyo Medical and Dental University), Japan. **Organizer:** Dr Mitsuaki Isobe (isobemi.cvm@tmd.ac.jp)
- **May 19-22, 2012. XXXI Annual Meeting of the European Section (will be held jointly with the ESC HFA).** Belgrade, Serbia. *Website:* www.escardio.org/congresses/hf2012/Pages/welcome.aspx
- **May 28-31, 2012. XXXIII Annual Meeting of the North American Section.** Banff, AB, Canada. **Organizer:** Dr Gary Lopaschuk (gary.lopaschuk@ualberta.ca)
- **June 30 - July 4, 2013. XXI World Congress of the ISHR.** San Diego, California. **See page 14**

(continued from page 10)

Dr Koch has also studied the role of GRK2 in other organs during heart failure progression and in a study published in 2007 in *Nature Medicine*, his lab defined a pathological role for this kinase in sympathetic nervous system regulation and catecholamine release from the adrenal gland. Most recently, Dr Koch's team, in a paper recently published in *Circulation Research*, has shown that GRK2 in the heart is not only important in chronic heart failure but its activity is pathological in the acute setting as it acts as a pro-death kinase in myocytes after ischemic injury.

In addition to landmark studies detailing the importance of GRK2 in the cardiovascular system, Dr Koch has also shown a second GRK, GRK5, to be critical. This includes demonstrating that this kinase

has the unique property to localize to the nucleus of myocytes where it exerts a novel, non-GPCR function as a Class II HDAC kinase to promote maladaptive cardiac hypertrophy. This was published in 2008 in *The Proceedings of the National Academy of Sciences, USA*. Concerning cardiac hypertrophy, Dr Koch's group, in a seminal paper published in *Science* in 1998, were the first to demonstrate that signaling through the heterotrimeric Gq was the common signaling trigger for pressure overload hypertrophy and inhibition of Gq could block both adaptive and maladaptive hypertrophy. The latter study above published in *PNAS* did indeed show that GRK5's pathological actions in the nucleus of myocytes followed Gq activation.

Finally, Dr Koch, widely regarded as a leader in cardiac signal transduction, is equally regarded as a leader and mentor of junior investigators. Over 40 Fellows have trained in his lab with several now supported by their own NIH grants in academic medicine. This is a source of great pride as he relishes mentorship and influencing the careers of young scientists. ■

PREVIOUS AWARD WINNERS

- 2002 Peter Carmeliet
- 2003 Issei Komuro
- 2005 Eric Olson
- 2006 Joseph Loscalzo
- 2009 Mathias Gautel
- 2010 Jeffery Molkentin
- 2011 Walter Koch



ISHR Outstanding Investigator Award

Nominations are currently being accepted for the **2012 Outstanding Investigator Award**.

The purpose of this award is to recognize an outstanding scientist who (i) is making major and independent contributions to the advancement of cardiovascular science, and (ii) is leading a growing research program likely to play a major role in the future. The main criteria for selecting awardees are scientific excellence, independence, and potential for future research contributions.

Details of the competition are available on the ISHR website (www.ishrworld.org) under the **ISHR Awards** tab.

Nomination materials must be received **no later than October 31, 2011.**

HEART NEWS AND VIEWS

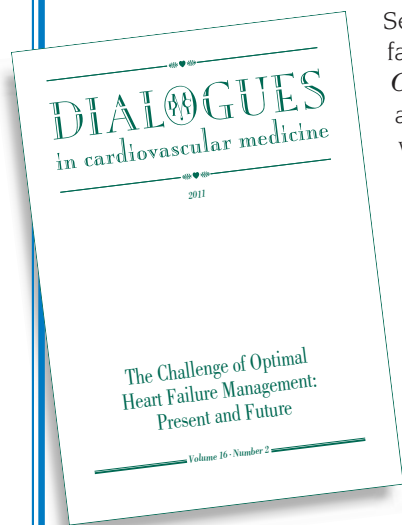
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The forthcoming issue, devoted to
THE CHALLENGE OF OPTIMAL HEART FAILURE
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will feature articles by:
**K. Swedberg; M. Komajda;
M. Cowie; K. Dickstein**

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