Celebrating physiological genomics at the 125th anniversary of the American Physiological Society

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THE PHYSIOLOGICAL GENOMICS (PG) Group of the American Physiological Society marked the 125th anniversary celebration of the American Physiological Society by organizing four exciting scientific sessions at the recently concluded Experimental Biology meeting 2012 held at the San Diego Convention Center. These included a cross-sectional workshop “Toolkit for genomic biomarker discovery by physiologists” chaired by Drs. Bina Joe and Lance Miller, a symposium on “Molecular and cellular therapy for cardiovascular disease” chaired by Drs. Zhongjie Sun and Stephen C. Mockrin, a featured topic on “Translational biomarkers of hypertension: Insights from animal models” chaired by Dr. Joe, and a special session, “Trainee highlights in physiological genomics” chaired by Drs. Jia Zhuo and Carol Moreno. The scientific impact of these four sessions was reflected through the active discussions that followed after each of these session presentations and from large scientific audiences including faculty members and postdoctoral and graduate trainees across all sections of the American Physiological Society.

Workshop

The cross-sectional workshop was aimed at providing methodological insights for physiologists interested in employing novel models and large-scale systems biology approaches as tools for their research. The five talks in this session were focused on large-scale chromatin immunoprecipitation (ChIP) sequencing, RNA sequencing, quantitative proteomics, and integrative systems biology for physiological signaling pathway modeling and on the methods to generate novel genetically engineered rat models. Dr. Jun Zhu from the National Heart Lung and Blood Institute (NHLBI) presented detailed methods for large-scale ChIP sequencing. Similarly, Dr. Mingyu Liang provided an equally informative talk on large-scale RNA sequencing. Both of the talks not only captured the “how-to” and “to-do” aspects for each of these techniques but also presented physiological data as examples emerging from the application of these methods. The application of a quantitative proteomic approach to discovering novel mechanisms of vasopressin biology was detailed by Dr. J. D. Hoffert. He explained the methods for large-scale quantitative proteomics with references to specific techniques using stable isotope labeling of amino acids in culture (SILAC) and isobaric tags for relative and absolute quantitation (iTRAQ). Using iTRAQ, Dr. Hoffert identified arginine vasopressin (AVP)-dependent changes in hundreds of phosphopeptides from rat inner medullary collecting ducts. By clustering results based on time and gene ontology terms (GO terms), Dr. Hoffert developed a novel and significantly augmented putative AVP-dependent signaling pathway. He and his colleagues are currently investigating the role of select phosphorylated proteins in AVP-dependent signaling using classic reductionist approaches. Dr. Lance Miller followed through on a similar experimental system but emphasized the integration of deep sequencing (i.e., RNA-seq and ChIP-seq) with quantitative proteomics. Clustering of RNA-seq data from various time points revealed two distinct temporal patterns of gene expression, i.e., early and late induction, while bioinformatic analysis of promoter elements suggests early- and late-induced genes are regulated by various different sets of transcription factors. This study was followed up using quantitative proteomic analysis to identify candidate transcription factors that translocated to the nucleus after administration of AVP. ChIP-seq was performed to identify genome-wide binding profile of a number of these candidate transcription factors. Thus, application of “-omics” in these studies led to the development of novel paradigms in AVP-dependent signaling and transcriptional regulation. Finally, Dr. Carol Moreno from the Medical College of Wisconsin presented the methods pertinent to the application of the zinc-finger nucleases based technology for generating custom genome-edited rat models. This method was recently recognized as the “method of the year” by Nature Methods (http://www.nature.com/nmeth/journal/v9/n1/full/nmeth.1852.html). The talk was regarded as being timely and informative and provided a great way for the meeting attendees to contemplate the inclusion of these models in their research endeavors.

Symposium

The symposium on “Molecular and Cellular Therapy for Cardiovascular Disease” attracted a large audience including cardiovascular physiologists, cardiologists, and molecular biologists. There is currently intense interest in the development of molecular therapies in this area, and the symposium participants outlined a wide array of novel approaches. Molecular and cellular therapy is a new and exciting area of cardiovascular medicine that aims to apply molecular and cellular approaches for the prevention and treatment of cardiovascular disease. As an emerging discipline, it has changed our thinking...
of treatment for cardiovascular disease and is providing great promise for the future. In this symposium, well-recognized experts in the field provided the audience with some of the most recent advances in the field of molecular and cellular therapy for cardiovascular disease. Dr. Mohan Raizada from the University of Florida presented a novel concept of a counterregulatory role of angiotensin converting enzyme 2 (ACE2), a newly discovered member of the renin-angiotensin system (RAS), in balancing the vasoconstrictive, proliferative, and fibrotic axis of the RAS. The proof of this new concept was presented by evidence that ACE2 activation by novel compounds or its overexpression by gene transfer or engineered stem cells produces beneficial outcomes in cardiovascular disease. Dr. Zhongjie Sun from the University of Oklahoma reported, for the first time, that deficiency of klotho, a recently discovered antiaging gene, is an etiological factor for endothelial dysfunction, hypertension, and kidney damage. Dr. Sun provided important evidence that demonstrated that in vivo expression of klotho by AAV2 delivery of klotho gene is an intriguing and promising approach for cardiovascular dysfunction and kidney damage. Dr. Yasuhiro Ikeda shared his success in sustained and cardiac-specific overexpression of B-type natriuretic peptide (BNP) and guanylyl cyclase agonist (CD-NP, cenderitide) using myocardium-trophic AAV9. Overexpression of BNP and CD-NP improved left ventricular function, attenuated cardiac hypertrophy, and extended survival in spontaneously hypertensive rats. Dr. Andre Terzic gave an impressive update on the current status and future directions in stem cell therapy for heart disease. He provided convincing evidence to suggest that stem cell therapy resulted in the generation of new cardiomyocytes and improved heart function in the infarcted heart. Finally, Dr. Stephen C. Mockrin from NHLBI introduced NHLBI resources to the audience. NHLBI offers extraordinary opportunities and provides unique resources to advance molecular and cellular therapies. Dr. Mockrin’s talk focused on how the
NHLBI is working to fill the funding gaps that have been identified in the transition of discoveries from bench to bedside. The details on some of these resources are available at the NHLBI website (http://www.nhlbi.nih.gov/).

**Featured Topic**

The featured topic “Translational biomarkers of hypertension: insights from animal models” showcased the integration of the rat as a model organism not only for identifying homologous genetic elements controlling blood pressure but also for validating the results from genome-wide association studies (GWAS) for hypertension and renal disease in humans. Dr. Howard Jacob from the Medical College of Wisconsin shared the success from his team in pioneering the application of the zinc-finger nuclease technology and creating the first large-scale set of 110 mutant rat strains to validate genes identified by the GWAS for hypertension and related diseases. The importance of the design of using the Dahl S rat genome as a genetically sensitive strain to the development of hypertension was recognized as one of the factors contributing to the successful validations of the GWAS genes in rat ZFN-mutant models. The gene Sh2b3 was prominently mentioned as being one of the first genes identified using GWAS to be also validated as a gene modulating blood pressure in rats. Dr. Bina Joe’s talk took the opposite tactic of presenting data on the positional cloning approaches in hypertensive rat models that have found parallel linkage or associations in genetic studies of human cardiovascular disease. These included variations within protein-coding genes Cyp11b2 and Adamts16. Dr. Joe also discussed the value of “extreme mapping” to resolutions of a few kilobases as not only yielding positional protein-coding candidate genes but also adding valuable data to enhance our current appreciation for epistasis and regulation of hypertension by noncoding elements. It is to be noted that these data from rat model studies are in line with the current thoughts on “missing heritability” in human complex traits (Zuk O, Hechter E, Sunyaev SR, Lander ES. *Proc Natl Acad Sci USA*: 109: 1193–1198, 2012). Dr. R. D. Wainford presented a case for the gene Gnai2 as a candidate biomarker for hypertension that determines salt resistance versus salt sensitivity in rat models.

**Trainees’ Highlights Session**

The PG Group was strongly committed to support the participation of junior faculty members, postdoctoral fellows, and graduate students to present their research at Experimental Biology 2012. For the first time, the PG Group obtained the generous sponsorship of Sigma-Aldrich and Kent Scientific Corporation for several trainee awards at Experimental Biology 2012. This year, the PG Group Steering Committee selected 11 from 66 excellent abstracts submitted by trainees for various sessions of the American Physiological Society for oral presentations. An important feature of this year’s featured topic and trainees’ highlights sessions is that the top three trainee presentations in each session were recognized with research awards. The selections for these awards were based on the ranking of their abstracts and presentations judged by several members of the PG Group Steering Committee. All other trainees who were chosen for oral presentation at Experimental Biology 2012 received a research recognition award to recognize their participation in physiological genomics research. The session chairs, Drs. Jia Zhuo and Carol Moreno, led an interactive and diverse trainee session. The PG Group is very grateful to those volunteers for their contribution to the success of PG Group’s organized sessions and to Sigma-Aldrich and Kent Scientific Corporation for generous corporate support for trainee awards.

**Henry Pickering Bowditch Award**

Finally, to top it all, the PG Group was proud to be recognized by the American Physiological Society on its 125th anniversary with the prestigious Henry Pickering Bowditch Award to one of our active members, Dr. Mingyu Liang, from the Medical College of Wisconsin. Dr. Liang captivated the audience with his presentation on microRNAs and systems molecular medicine. (Figure 1 and 2)