Understanding renal and cardiovascular function through physiological genomics

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AS PART OF A CONTINUING EFFORT to integrate physiology and genomics, the American Physiological Society sponsored a meeting at the Riverfront Augusta Hotel in Augusta, Georgia, October 1–4, 2003, titled “Understanding Renal and Cardiovascular Function through Physiological Genomics.” Organized by David Pollock of the Medical College of Georgia, the meeting focused on consolidation of physiological genomics as a research field in its own right and on adaptation of the field of physiology to the genomic and proteomic era by successfully linking genes to complex physiological functions.

The conference successfully addressed the primary goal: to provide an opportunity for learning how new technologies, tools, and applications of genomics can be used by the physiologist to discover how genetic and environmental factors influence renal and cardiovascular function. The invited speakers represented a unique blend of experts that were able to communicate their knowledge of genomic approaches as a means of addressing important physiological and pathophysiological questions. Sessions focused on a variety of research topics, from gene expression and proteomics to signaling pathways, bioinformatics, and pharmacogenomics, and their application to cardiovascular and renal diseases in humans and research animals. Special emphasis was placed on the need for a systems biology approach to research, which is only possible through collaboration and formation of interdisciplinary research teams, and this generated lively discussion at the scientific sessions.

The opening symposium was an especially unique opportunity for students and trainees, because it dealt with how physiological genomics is being applied in the biotech and pharmaceutical industries in the context of career opportunities in the field. An exciting and diverse set of presentations were given by Una Ryan, President and CEO of Avant Immunotherapeutics, Joan Keiser, Director of Cardiovascular Pharmacology at Pfizer Global Research and Development, and Terry Bishop, Program Director for Training and Careers at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). Time was then allotted for individuals to break out into small group discussions with each of the speakers, which allowed students and trainees to have specific questions addressed.

The scientific portion of the program began with state-of-the-art lectures from four preeminent scientists, Fredrich Luft, Chief of Nephrology and Hypertension at Humboldt University of Berlin, provided a fascinating example of the how genetic analysis can be used in a clinical investigation of human hypertension. He presented the case of a Mendelian form of hypertension associated with brachydactyly, in which his laboratory mapped the genes for this disease to chromosome 12p. They narrowed the region to 3 cM and screened the coding region of the candidate genes in the area. Because these genes revealed no positive findings, they performed cytogenetic studies to screen for chromosomal rearrangements within the segment. Using interphase fluorescent in situ hybridization (FISH) with bacterial artificial chromosome (BAC) probes from the linked region, they found that rearrangement mutations had occurred in affected patients that could induce gain of function in some of the candidate genes.

Allen W. Cowley, Jr., Chair of the Department of Physiology at the Medical College of Wisconsin and Editor-in-Chief of Physiological Genomics, discussed how complex diseases such as hypertension can be deciphered by the use of genetically designed rats and high-throughput phenotyping. He talked about the pathway for gene discovery, from genetic linkage through development of consomic and congenic strains of rats, as well as candidate gene testing, emphasizing the need for hypothesis-driven physiology in the selection of candidate genes. Elizabeth Nabel, Scientific Director of Clinical Research at the National Heart, Lung, and Blood Institute, gave an excellent summary of how her laboratory has used a three-prong approach to study arterial wound repair: in vivo gene deletion, molecular biology, and genomic/proteomics.

Josephine Briggs, head of the Division of Kidney, Urologic, and Hematologic Diseases at NIDDK, gave an overview of the NIH Roadmap for Medical Research. This is a series of initiatives launched recently by the NIH to transform the nation’s medical research capabilities and speed the movement of research discoveries “from the bench to the bedside.” To integrate knowledge from molecular and cell biology, Dr. Briggs said, the research community needs wide access to technologies, databases, and other scientific resources.

The second day of the meeting began with a session titled “Gene Expression, Proteomics and Pharmacogenomics.” In this session, the speakers presented some interesting examples of how the new tools of genomics are being applied to understand renal and cardiovascular disease. Jin-Xiong She (Medical College of Georgia) described the establishment of biomarkers for predicting the progression of type I diabetes and its kidney complications. His laboratory analyzed tissue samples by microarray and new techniques such as protein microarrays, mass spectrometry, and bioinformatics for clustering, to show that expression profiling allowed them to group patients into two main categories that correlated with the progression of the disease. W. Marston Linehan (National Cancer Institute) talked about the discovery pathway in clinical research and how the sequence goes from clinical evidence, through genetic linkage, physical mapping, and finally sequencing of candidate genes. From a clinical standpoint, it is most important to understand the pathophysiology and the downstream effectors in order to develop treatment for diseases. John Yates
(Scripps Research Institute) described methods that have been developed to characterize elements of the proteome in cells and organelles. These include protein identification, regulation (posttranslational modifications), dynamics (quantification), and validation (genetics, RNA, siRNA), which could ultimately aid translation of technology development to biological development. The next speaker, Kelly Frazer (Perlegen Sciences), described how identification of single-nucleotide polymorphisms (SNPs) can be used to define the haplotype structure of a population, which then provides a powerful means for identifying genetic determinants of common human disease. Guidelines for a systems biology approach through the use of RNA expression was the topic of the presentation by Steve Gullans (Harvard University). Gullans suggested that researchers consider that spatiotemporal patterns of gene expression are not a reflection of the activation of pathways, but rather a reflection of gene complex interactions. Systems biology requires a global, dynamic, multi-responsive approach with multiple level of analysis (DNA, RNA, protein) that is quantitative, valid, and reproducible.

Arguably one of the biggest challenges in the emerging field of physiological genomics is how to handle the tremendous amount of new information that can be generated by microarrays and other high-throughput approaches. Therefore, it was quite useful that the meeting included a workshop on bioinformatics. Chaired by Richard McIndoe (Medical College of Georgia), this workshop provided something of a beginner’s lesson on the challenges. McIndoe shared insights into how a laboratory could use available bioinformatics resources to manage and analyze the increasing amount of data generated in contemporary research. Peter Tonellato (Medical College of Wisconsin) talked about how bioinformatics can fulfill the needs of high-throughput research by building accessible databases and analytical tools to facilitate the understanding of multi-gene interactions within the context of physiology.

The difficulties involved with translating expression data generated by DNA arrays into biological knowledge were discussed by Roger Bumgarner (University of Washington). This was particularly useful, given the large number of physiologists who are using microarrays as a foray into the field of physiological genomics. He noted that the difficulty in giving biological meaning to data can be due to a number of factors, including variations in experimental design and application (replicates), an inability to extract statistically meaningful data from experiments, difficulties in linking the data to other sources of information (function, references, etc.), complications with sharing data from different sources and platforms, problems with the initial experimental design, and insufficient allocation of resources to data analysis. He recommended the use of oligos instead of cDNA, for reducing the number of false-positive and false-negative results due to cross hybridization, and the use of replicates, especially the use of different platforms, to increase reliability. He also emphasized the importance of experimental design and suggested combining genetic mapping with microarrays, as the intersection of results will reduce the list of candidate genes.

The next two sessions at the meeting provided more specific examples of what is meant by physiological genomics research. Curt Sigmund (University of Iowa) demonstrated the utility of gene-targeting approaches for dissecting the significance of genes expressed in different tissues and in specific cell types. Howard Jacob (Medical College of Wisconsin) discussed the need for basic research to improve experimental models of disease to more accurately reflect human disease and to facilitate applicability and translation from animals to humans. Peter Doris (University of Texas-Houston) explained how to obtain global insights into complex diseases such as polygenic hypertension using a battery of techniques including expression arrays, proteomic approaches, sequence analysis, and positional testing by linkage studies in F2 populations of mice.

Harold Snieder (Medical College of Georgia) presented a gene-environment model of stress-induced hypertension that explains how repeated exposure to stress, in combination with genetic susceptibility, might lead to the development of hypertension. Erwin Bottinger (Albert Einstein College of Medicine) gave an interesting presentation on how different diabetic mouse models were used to reach a global view of the pathogenesis of diabetes nephropathy. He provided rationale for how genes and pathways that are identified in mice as important in the pathogenesis and progression of diabetic nephropathy can be further evaluated as diagnostic tools or potential drug targets in human disease. David Wasserman (Vanderbilt University), Jurgen Schermermann (National Institutes of Health), and Jeff Sands (Emory University) each discussed how they are using specific gene targeting approaches in vivo to understand specific renal vascular and tubular functions.

A high level of enthusiasm was clearly evident for two poster sessions and two oral free communication sessions that were based on submitted abstracts. These less structured portions of the program were one of the strengths of the conference, in that they allowed opportunities for open exchange of ideas and allowed a greater number of younger investigators to present their work. The submitted abstracts included a large number of studies involving genetically manipulated animals. Thus it is clear that the scientific community considers physiological genomics to include classic approaches to ask new questions.

Abstracts were grouped under the headings of Gene Regulation in the Vascular System, Cardiac and Vascular Signaling Pathways, Obesity and Diabetes, Neural and Stress-Induced Factors, Genetic Mechanisms of Hypertension, Renal Gene Expression, and Renal Mechanisms. Free communications sessions were titled Genomic and Proteomic Analysis and Functional Studies in Genomics.

Overall, the conference can be considered a success, with over 150 people registered. A very large number of these attendees were students and trainees. This conference provided a valuable service and met its goal of bringing together scientists working in diverse areas of physiological genomics. Conferences such as these will help define the field and shape our thinking about how new technologies and experimental approaches can be used to answer questions of how genes influence physiological systems. An important component in the success of the conference was unrestricted educational grants from AstraZeneca, Bio-Rad Laboratories, Fisher Scientific, Medical College of Georgia, and Merck and Co., Inc.