Meeting report: *Physiological Genomics of Cardiovascular Disease: from Technology to Physiology*

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A THREE-DAY MEETING entitled “Physiological Genomics of Cardiovascular Disease: from Technology to Physiology,” sponsored by the American Physiological Society, was held at the Cathedral Hill Hotel in San Francisco, CA, February 20–23, 2002.¹ The conference was organized by Curt D. Sigmund of the University of Iowa. The conference began with a keynote address by Francis Collins of the National Institutes of Health on the impact of genomics on the practice of medicine. Subsequent days featured sessions on Comparative Genomics; Patterns of Gene Expression and Bioinformatics; Cardiomyopathy and Arrhythmias; Cardiovascular Development and Function; Pharmacogenetics; and Gene and Molecular Therapies.

Francis Collins’ keynote talk addressed one of the repeated themes of the conference: that a thorough knowledge of the complex interaction between genotype and phenotype was required to have the greatest impact on medicine and disease prevention. Throughout the conference, speakers detailed the uses of comparative genomics, bioinformatics, expression profiling, and genome association studies to elucidate the genomics of cardiovascular disease. Particular talks representative of each section are highlighted herein.

In the session on Comparative Genomics, Edward M. Rubin (Lawrence Berkeley National Laboratory) described using sequence alignment tools to uncover biological similarities between different species. For example, a new gene, Apo AV, was discovered in an analysis of the human chromosome 11 apolipoprotein gene cluster, on the basis of sequence similarity between human, rabbit, and mouse DNA. Knocking out this gene in mice led to higher triglycerides. Several separate, subsequent association studies demonstrated an association of certain Apo AV polymorphisms with increased plasma triglycerides in humans. Given the degree of sequence conservation among vertebrates, the question arises to how different animals exhibit different physiological conditions with the same starting proteins. In another example, Dr. Rubin described a case of convergent sequence evolution in the apolipoprotein (a) gene, Apo (a), between humans and hedgehogs. Individuals with high levels of Apo (a) are at increased risk for atherosclerosis. Interestingly, the gene is found in old world monkeys, great apes, hedgehogs, and humans, but not in new world monkeys, lemurs, or mice. Phylogenetically, the presence of Apo (a) in hedgehog would suggest that the gene was repeatedly lost in several of the primate lineages, or that the gene was independently derived in the hedgehog lineage. A detailed sequence analysis suggests convergent evolution, given that human and hedgehog Apo (a) have separate, duplicated fibrin binding domains also found in the plasminogen gene of each.

Isaac Kohane (Children’s Hospital, Boston, MA, and Harvard Medical School) gave a presentation in the session on Patterns of Gene Expression and Bioinformatics on the importance of separating signal from noise in microarray data. He brought up a number of thought-provoking examples of how low-level gene expression is vulnerable to noise. For example, there may be periodicity in the intensity of spots on a microarray brought about by variability in the pins that deposit oligonucleotide probes on the array. He urged caution in interpreting gene expression data and made recommendations to cope with current limitations. One recommendation was to use a decision-theoretic approach to determine whether particular genes whose expression appeared significantly different between control and experimental conditions were worth further study. In addition, the recommendation was made to set a range of insignificance, i.e., to indicate a minimum level of expression below which fluctuations in intensity would be considered too noisy. Dr. Kohane’s talk sounded an important cautionary note with relevance to the entire research symposium, since so much of the
research presented relied upon modern analytical methods of functional genomics.

One of the speakers in the Cardiomyopathy and Arrhythmias session, Christine Seidman (Harvard Medical School), compared genetic studies of hypertrophic and dilated cardiomyopathy (HCM and DCM) in mice to address the question of whether the two pathologies are points along the same pathway of disease progression. Mutations in the sarcomeric protein myosin heavy chain (MHC) can lead to both DCM and HCM. One mouse model of left ventricular hypertrophy involves a mutation in the myosin heavy chain, αMHC \(^{403V/+}\), whose pathology can be worsened by altering environmental factors such as exercise stress, drugs, or aortic banding. For example, exercise stress induced by swimming, induction of pressure overload via aortic banding, and treatment with cyclosporin all accelerate cardiac hypertrophy in this particular mutant strain. Although in these cases a “progression” to DCM is not observed, Dr. Seidman noted that the dosage of sarcomeric protein mutation dictates the resulting phenotype: heterozygous defects seem to produce HCM, and homozygous defects seem to produce DCM.

In the session on Cardiovascular Development and Function, Mark Fishman (Massachusetts General Hospital, Boston, MA) described zebrafish research to study cardiovascular development and function. Zebrafish embryos are transparent, allowing for easy identification and characterization of cardiovascular mutants. Dr. Fishman described mutations in genes that affect ventricle differentiation. Cardiovascular genes of “model organisms” such as the zebrafish and *Drosophila* often have homologs in humans and therefore can provide important insight into conserved molecular pathways. For example, the pickwick mutation affects the titin gene, whose protein product forms the spring of the sarcomere. It was recently demonstrated that a mutation in titin causes dilated cardiomyopathy in humans. A similar disease effect is observed in zebrafish.

In the Pharmacogenetics session, Allen Roses, of GlaxoSmithKline, gave examples of how a pharmaceutical company can successfully incorporate pharmacogenetics into the drug development process. Pharmacogenetics examines the variability of drug response due to inherited characteristics in an individual. With the availability of whole genome single nucleotide polymorphism (SNP) maps, it will soon be possible to create an SNP profile for patients who experience an adverse event or who clinically respond well to a drug. With this knowledge, physicians will be able to provide a greater degree of personalized medicine by prescribing drugs more accurately based on a patient’s predicted response. Dr. Roses noted that GlaxoSmithKline has recognized the important role of pharmacogenetics in the drug development process, and he described several examples to illustrate this point. A clinical trial for the drug tranilast, used to treat restenosis after percutaneous transluminal coronary revascularization, led to hyperbilirubinemia in 4% of patients. An association study identified (TA)\(_n\) as a susceptibility polymorphism for Gilbert’s syndrome, for which the tranilast hyperbilirubinemia patients were uniformly homozygous. This research was initiated and completed over a 3-mo period. As another example, Dr. Roses described the HIV medication abacavir. Five percent of patients experience a hypersensitivity reaction to the drug, and the company researched the possibility of a genetic link. What was found confirmed a “proof of principle” that genetic factors were linked to hypersensitivity to abacavir. Results from this pharmacogenetic study may lead the way to minimizing the risk-benefit ratio for abacavir by identifying those patients with predisposing factors and thereby reducing the risk of an adverse event.

In the section on Gene and Molecular Therapies, Robert Simari (Mayo Clinic, Rochester, MN) spoke on the challenges of translating advances in gene transfer into gene therapy. Researchers are exploring alternatives to viral vectors in order to avoid associated toxicity and the potential for mistargeting. The goal is successful delivery of transgenes that affect vascular function and structure to alter the course of cardiovascular disease. One example Dr. Simari provided detailed sonoporation, or ultrasound-induced gene transfer. Since a collapsing microbubble forms a jet which can act as a microinjector, ultrasound, used in conjunction with microbubbles containing particular transgenes, might target specific tissues effectively. So far, sonoporation has been used to deliver a green fluorescent protein (GFP) transgene to the triceps muscle of rats; in the future, such a technique could be used in targeted arterial delivery.

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