Seminar:
“Using Genetics to Identify the Molecular Mechanisms of Atrial Fibrillation”

Abstract:
Atrial fibrillation (AF) affects over 3 million individuals in the US and 4.5 million individuals in Europe. In addition, AF is associated with an increased risk of stroke, dementia, heart failure, death and health care costs. Many AF risk factors have been identified including aging, cardiovascular disease, and family history. Although heritable forms of AF were previously considered rare, we have established evidence of substantial AF heritability over the last decade.

Genome-wide association studies (GWAS) provide a powerful tool to identify common variants underlying disease risk. In 2007 a GWAS for AF identified a locus on chromosome 4q25. Later that year, we organized the AFGen Consortium, which presently consists of investigators from over 30 studies to further the discovery of the genomic basis of AF. To date, at least 30 AF loci have been identified that broadly implicate genes related to cardiopulmonary development, cardiac-expressed ion channels, and cell signaling molecules.

However, despite rapid progress in identifying common genetic variants associated with AF by GWAS, many questions remain. What are the causal variants at AF GWAS loci? What are the molecular pathways that predispose carriers of the rare alleles to AF? How do these variants help inform the management of AF?

In the upcoming years major projects will include 1) Performing large-scale whole genome sequencing in thousands of individuals with early-onset AF, 2) GWAS genotyping and meta-analyses with over 60,000 AF cases, 3) Identification of enhancers at AF risk loci by developing high-resolution epigenetic maps from the human left atrium, 4) Characterizing the molecular mechanisms promoting AF in mouse knockout models of the genes at AF GWAS loci, and 5) Targeting the genes at AF GWAS loci for therapeutic development.

Ultimately, we believe that our collaborative translational approach will facilitate a greater understanding of the molecular basis of this common and morbid arrhythmia. Identification of causative variants for AF may enhance risk stratification, and will provide preventive and therapeutic targets for drug discovery in the broader scientific and pharmaceutical community.