Geoffrey W. Abbott  
Professor & Vice Chair  
Department of Pharmacology  
Professor, Physiology & Biophysics  
University of California, Irvine, School of Medicine

Seminar Title  
K+ Channel – Linked Arrhythmias: Lessons from a Decade of Studying KCNE Knockout Mice

Abstract  
Coronary Artery Disease (CAD) leads to more deaths in the U.S. and globally each year than any other single cause of death. An estimated half of CAD cases involve genetic predisposition; reduction of other risk factors can reduce CAD mortality and morbidity by >30%. The major challenge now is to develop more comprehensive prevention and treatment strategies for both genetic and environmental risk factors, necessitating a better mechanistic understanding of CAD.

Another form of fatal heart disorder, Sudden Cardiac Death (SCD), accounts for ~1000 deaths per day in the U.S. SCD is thought to require an electric substrate, an ischemic substrate, and perhaps a trigger. Despite great leaps in our understanding of SCD, there is still much to learn. Because most of the 25 genes linked to SCD also serve roles outside the heart, it makes sense to consider how disruption of these extracardiac roles impacts SCD and arrhythmogenesis. Many SCD-linked genes encode ion channel pore-forming (α) subunits, but the rest encode proteins that regulate them. It is thus crucial to understand the biology and pathobiology of macromolecular ion channel complexes in their entirety.

In the Abbott lab, we focus primarily on discovering novel roles and functions for the KCNE family of single-transmembrane domain potassium channel β subunits. Much of this research has been directed toward discovering the pathologic manifestations arising from targeted deletion of KCNE genes in mice. All five of the KCNE genes are expressed in both human and mouse heart, and disruption of each gene has been linked to cardiac rhythm disturbances in either species. While much of this arises from direct impairment of KCNE-containing, cardiomyocyte ion channel complexes, some sources of KCNE-linked arrhythmogenesis lie outside the heart. In addition, KCNE gene disruption can even cause CAD, providing a genetic link between this prevalent disease and SCD. Our findings from a decade of studying KCNE gene knockout mice suggest that even monogenic cardiac arrhythmias can be highly complex, multi-faceted syndromes involving multiple organ systems.