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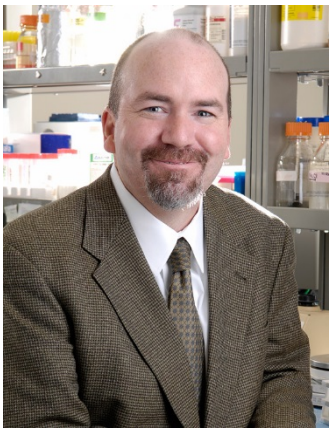

Seminar:
Defining New Pathways Underlying Human Arrhythmia

Abstract:
Our research is focused on the mechanisms underlying the targeting and regulation of membrane-associated (ion channels, transporters, receptors) and signaling proteins in cardiac and other excitable cells. In particular, we are interested in the role of membrane-associated ankyrin and spectrin family of polypeptides in the targeting and function of ion channels and transporters as well as kinases and phosphatases. A primary focus of the lab is the role of the ankyrin-G-based pathway for targeting voltage gated sodium channels to the intercalated disc of cardiomyocytes. We have discovered a direct requirement of ankyrin-G for Na channel targeting and have linked human Na channel arrhythmia mutations with loss of ankyrin-G binding, and Na channel targeting resulting in defects in Na channel function and myocyte excitability. A second line of work in the lab establishes that loss-of-function mutation in ankyrin-B is the basis for a human cardiac arrhythmia syndrome associated with sinus node dysfunction, repolarization defects, and polymorphic tachyarrhythmia in response to stress and/or exercise ("ankyrin-B syndrome"). Additionally, our work revealed that reduction of ankyrin-B in mice results in reduced levels and abnormal localization of Na/Ca exchanger, Na/K ATPase, and InsP3 receptor at T-tubule/SR sites in cardiomyocytes and leads to altered Ca2+ signaling and extrasystoles that provide a rationale for the arrhythmia. These studies establish a physiological requirement for ankyrins and spectrins in localization of a variety of ion channels in excitable membranes in the heart and demonstrate a new class of functional 'channelopathies' due to abnormal cellular localization of functionally-related ion channels and transporters. More recently, we have developed a third line of research in the lab focused on the molecular mechanisms underlying kinase and phosphatase targeting in excitable cardiomyocytes. Specifically, work from our lab has shown the importance of CaMKII and PP2A targeting for myocyte and cardiac function.