“Structure and function of G protein-sensitive K^+ channels and drug discovery”

Diomedes Logothetis, Ph.D.

Professor Emeritus, Northeastern University

Co-Founder and Acting CEO, ALLION Therapeutics, LLC

Abstract

Ion channels mediate the movement of ions across cell membranes down their electrochemical gradients, regulating essential physiological processes in both excitable and non-excitable cells. Their functions extend from controlling neuronal excitability and cardiac rhythm to regulating epithelial fluid transport, cell proliferation, and numerous other cellular activities. Consequently, ion channel dysfunction is implicated in a broad spectrum of human diseases, including epilepsy, chronic pain, addiction, anxiety, cardiac arrhythmias, cystic fibrosis, and cancer.

G protein-gated inwardly rectifying potassium (GIRK) channels are key regulators of cellular excitability, coupling extracellular signals received by G protein-coupled receptors (GPCRs) to changes in membrane potential through G protein-mediated signaling. In this seminar, I will present new atomic-resolution structures of the principal neuronal (GIRK1/2) and cardiac (GIRK1/4) heteromeric channels, highlighting insights into their molecular architecture, gating mechanisms, and allosteric regulation. I will then discuss how these structural insights, combined with computational approaches and functional studies, are guiding the discovery and optimization of selective small-molecule allosteric modulators. Particular emphasis will be placed on the development of neuronal GIRK channel activators as a novel therapeutic strategy for rare and common forms of epilepsy.