

Structure-function studies of signal transductions at cellular surface and downstream level; for targeted drug development

Project Investigator: Pramod Kumar, Ph.D., pkumar@cshl.edu, Cold Spring Harbor Laboratories, New York, USA.

Abstract: The signal transduction processes are critical phenomenon, largely originates from cell surface, followed by the downstream signal cascade, that ultimately converge to the gene transcription to regulate the homeostasis of life. The synaptic transmission is one of the highly specialized and fastest form of signal transduction occurs at excitable cell surfaces. This form of signal transduction largely mediated through Ligand-Gated Ion-Channels (LGICs) for sub-second responses. Along with the synaptic communication, almost every form of signal transduction ultimately regulated by the feedback loops of spatiotemporally regulated transcription machinery. Any deregulation among these steps cause multitudes of neurological and cancerous pathologies. Despite serving as primary target for several drugs and pharmacological agents, the structure function underpinning of these neuro-receptors and transcription assemblies largely have remained unknown and controversial. Harnessing the advancements of integrative structural biology—different forms of Cryogenic Electron Microscopy (Cryo-EM) imaging; atomic level by single particle Cryo-EM, cellular and tissue level by Cryo-Electron Tomography (Cryo-ET), x-ray crystallography, and the recent integration of highly accurate prediction of structures by AlphaFold—and biophysical technique, I will present my recent work on selective perturbation of LGIC ionic conductance in lipid dependent manner and their future applications. Moreover, forking from cell surface receptor to nuclear receptor, I shall also usher my current project on understanding nuclear receptors to find druggable sites.