THE SUNNEY AND IRENE CHAN LECTURE 2024

Lipid Signals in Immunity and Cancer: Insights from Single Molecule Biophysics

Date: 26 September 2024 (Thu)
Time: 4:30 PM – 5:45 PM
Venue: Mong Man Wai LT2

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Abstract

Lipid signaling pathways on cell membrane surfaces control a wide array of cell processes in health and disease. These pathways begin with cell surface receptors or intracellular sensors that activate lipid kinase enzymes on the target membrane. The kinases, in turn, generate signaling lipids that diffuse in the membrane plane, recruit downstream signaling proteins, and trigger a cascade of pathway activation and information transfer. My talk will describe our recent studies of three lipid signaling pathways central to immune cell migration, engulfment of pathogens, cell growth and renewal, and oncogenesis. Our approach begins by reconstituting each signaling pathway from purified components on the target membrane. Subsequently, we use tools of single molecule biophysics developed by our lab and others to monitor the membrane-bound signaling proteins and directly measure their 2-dimensional diffusion, interactions, activation, and output lipid signals in real time. This approach provides fundamental new insights that expand our basic understanding of lipid signaling on molecular, dynamic, and mechanistic levels. Such understanding may also facilitate new therapeutics that target defective lipid signaling in autoimmune and inflammatory disorders, and in many human cancers.

Biography

Joseph J. Falke was a National Merit Scholar at Earlham College where he received his B.A in Chemistry in 1978 with admission to Phi Beta Kappa Honor Society. He was a National Science Foundation Graduate Fellow in the laboratory of Sunney I. Chan at Caltech where in 1984 he completed his Ph.D. and received the McKoy Award for Outstanding Ph.D. Thesis in Chemistry. His Ph.D. research with Chan developed and applied a 35Cl NMR approach to elucidate structural and mechanistic features of the human red blood cell membrane anion exchange transporter (Band 3 / AE1).Subsequently, from 1985-87 he was a National Institutes of Health Postdoctoral Fellow in the laboratory of Daniel E. Koshland, Jr. at UC Berkeley where he began the development of site-directed cysteine and disulfide methods and applied them to the study of bacterial chemoreceptors. In 1987, Falke started his independent laboratory at the University of Colorado, Boulder in the Department of Chemistry and Biochemistry. In 1999 he became Full Professor and founded the University of Colorado Interdepartmental Molecular Biophysics Program with 43 member laboratories in 5 departments, serving as Director from 1999-2024 and now as Co-Director. In 2001, he was Chair of the Annual Biophysical Society Meeting (Boston), was elected Society President in 2007, and was named Society Fellow in 2015.

Since its inception, the Falke Laboratory has developed new physical/chemical methods and has used them to probe structure, dynamics and mechanism in membrane-based cell signaling pathways. Early studies applied site-directed cysteine and disulfide engineering and other biophysical-biochemical approaches to investigate bacterial chemoreceptors and their receptor-kinase lattice. This work revealed the piston transmembrane signaling and electrostatic adaptationmechanisms of bacterial chemoreceptors, as well as the ultrastability of their receptor-kinase lattice. The next phase of research developed FRET, EPR and EPR-guided molecular dynamics methods to investigate two membrane targeting domains each found in hundreds of human signaling proteins: the Ca2+-activated C2 domain and the PIP-lipid sensing pleckstrin homology (PH) domain. These efforts yielded C2 and PH domain membrane-binding thermodynamics, kinetics, lipid specificities, docking geometries, and 2-D surface search mechanisms.

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