EARL W. SUTHERLAND LECTURE

The Earl W. Sutherland Lecture Series was established by the Department of Molecular Physiology and Biophysics in 1997 to honor Dr. Sutherland, a former member of this department and winner of the 1971 Nobel Prize in Physiology or Medicine. This series highlights important advances in cell signaling.

THE Flexner DISCOVERY LECTURE SERIES

Upcoming Discovery Lecture:

PAUL TANG, M.D., M.S.

Vice President, Chief Health Transformation Officer, IBM Watson Health

Board-certified practicing internist, Palo Alto Medical Foundation

April 12, 2018
208 Light Hall / 4:00 P.M.

THE Flexner DISCOVERY LECTURE SERIES

EARL W. SUTHERLAND LECTURE

SPONSORED BY:
THE DEPARTMENT OF MOLECULAR PHYSIOLOGY AND BIOPHYSICS

BRIAN KOBILKA, M.D.

NOBEL PRIZE WINNER IN CHEMISTRY, 2012

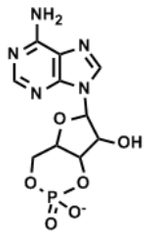
STRUCTURAL INSIGHTS INTO THE DYNAMIC PROCESS OF G PROTEIN COUPLED RECEPTOR ACTIVATION

APRIL 5, 2018
3:00 P.M.
208 LIGHT HALL

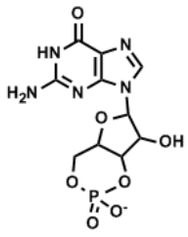
VANDERBILT UNIVERSITY MEDICAL CENTER

EARL W. SUTHERLAND, 1915-1974

Earl W. Sutherland grew up in Burlingame, Kansas, a small farming community that nourished his love for the outdoors and fishing, which he retained throughout his life. He graduated from Washburn College in 1937 and then received his M.D. from Washington University School of Medicine in 1942. After serving as a medical officer during World War II, he returned to Washington University to train with Carl and Gerty Cori. During those years he was influenced by his interactions with such eminent scientists as Louis Leloir, Herman Kalckar, Severo Ochoa, Arthur Kornberg, Christian deDuve, Sidney Colowick, Edwin Krebs, Theodore Posternak, Mildred Cohn, Victor Najjar, Joseph Larner and many others. Dr. Sutherland accepted the Chairmanship of Pharmacology at Western Reserve in 1953. It was there that he discovered cyclic AMP and demonstrated its role as the intracellular mediator of the epinephrine stimulation of liver glucose output. These studies provided the basis for formulation of the "Second Messenger" hypothesis for signal transduction. While at Western Reserve, he interacted with Theodore Rall, Joseph Larner, William Butcher and Alan Robison. Dr. Sutherland joined the Vanderbilt Department of Physiology in 1963 where he continued his work with Butcher and Robison and began collaborations with Charles Park, Grant Liddle, and Joel Hardman among others. This group demonstrated that in addition to its role in the actions of epinephrine, cyclic AMP is also the intracellular mediator of the effects of many other hormones on processes such as heart contraction, steroid release, fat breakdown, and blood pressure. They also suggested that cyclic GMP might serve as a second messenger. Dr. Sutherland's research on defining the biochemical basis for signal transduction pathways resulted in the discoveries of many enzymes, regulatory pathways, and pharmacological mechanisms. He was the first to resolve the molecular pathway of the action of a hormone and maintained a keen interest in disease mechanisms. Dr. Sutherland was a member of the National Academy of Sciences, the American Academy of Arts and Science, Alpha Omega Alpha, the American Society of Biological Chemists and many other scientific societies. He was awarded many prizes for his remarkable discoveries including the Banting Memorial Lectureship and Medal, the Sollman Award, the Gairdner Award, the National Medal of Science, and the Lasker Award. He was awarded the Nobel Prize in Physiology or Medicine in 1971.



cAMP



cGMP

BRIAN KOBILKA, M.D.

NOBEL PRIZE WINNER IN CHEMISTRY, 2012;

HÉLÈNE IRWIN FAGAN CHAIR IN CARDIOLOGY,

PROFESSOR OF MOLECULAR & CELLULAR PHYSIOLOGY, AND PROFESSOR (BY COURTESY) OF CHEMICAL AND SYSTEMS BIOLOGY, STANFORD UNIVERSITY

MEMBER, HHMI

Brian Kobilka, M.D. is Professor of Molecular and Cellular Physiology, and Hélène Irwin Fagan Chair in Cardiology at Stanford University School of Medicine. He received a Bachelor of Science degree in Biology and Chemistry from the University of Minnesota, Duluth in 1977. He graduated from Yale University School of Medicine in 1981 and completed residency training in Internal Medicine at the Barnes Hospital, Washington University School of Medicine, St. Louis, Missouri in 1984. From 1984-1989 he was a postdoctoral fellow in the laboratory of Robert Lefkowitz at Duke University. In 1990 he joined the faculty of Medicine and Molecular and Cellular Physiology at Stanford University. Research in the Kobilka lab focuses on the structure and mechanism of action of G protein coupled receptors (GPCRs), which constitute the largest family of receptors for hormones and neurotransmitters in the human genome. GPCRs are the largest group of targets for new therapeutics for a very broad spectrum of diseases. In 2012, Kobilka was awarded the Nobel Prize in Chemistry for his work on GPCRs. He is a member of the National Academy of Sciences, the National Academy of Medicine, and the American Academy of Arts and Sciences.

STRUCTURAL INSIGHTS INTO THE DYNAMIC PROCESS OF G PROTEIN COUPLED RECEPTOR ACTIVATION

G protein coupled receptors (GPCRs) conduct the majority of transmembrane responses to hormones and neurotransmitters and mediate the senses of sight, smell, and taste. The ß2 adrenergic receptor (ß2AR), the M2 muscarinic receptor, and the mu-opioid receptor are prototypical Family A GPCRs. We have obtained three-dimensional structures of these receptors in inactive and active conformations, as well as a structure of the ß2AR in complex with the G protein Gs. Comparison of these structures provides insights into common mechanisms for propagation of conformational changes from the agonist binding pocket to the G protein coupling interface. Crystal structures of inactive and active states may give the impression that GPCRs behave as simple two-state systems. However, cellular signaling assays reveal that many GPCRs signal through more than one G protein isoform and through G protein independent pathways. This complex functional behavior provides evidence for the existence of multiple functionally distinct conformational states. We have used fluorescence, EPR, and NMR spectroscopy to study the dynamic properties of several GPCRs. I will discuss what we these studies have taught us about allosteric regulation of GPCR structure by G proteins and ligands.