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.

SPEAKERS IN THIS SERIES HAVE INCLUDED:

Edmond H. Fischer (1997)
Alfred G. Gilman (1999)
Ferid Murad (2001)
Louis J. Ignarro (2003)
Paul Greengard (2007)
Eric Kandel (2009)
Roger Tsien (2011)

FOR MORE INFORMATION, CONTACT:

Department of Molecular Physiology & Biophysics
738 Ann and Roscoe Robinson Medical Research Building
Vanderbilt University Medical Center
Nashville, TN 37232-0615
Tel 615.322.7001
Angie.pernell@vanderbilt.edu

THE Flexner DISCOVERY LECTURE SERIES

EARL W. SUTHERLAND LECTURE

SPONSORED BY:
DEPARTMENT OF MOLECULAR PHYSIOLOGY AND BIOPHYSICS

MICHAEL S. BROWN, M.D

NOBEL LAUREATE IN PHYSIOLOGY OR MEDICINE 1985

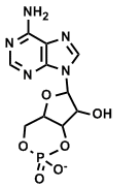
SCAP: ANATOMY OF A MEMBRANE STEROL SENSOR

APRIL 25, 2013
4:00 P.M.
208 LIGHT HALL

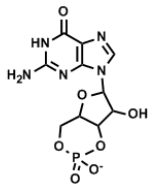
VANDERBILT UNIVERSITY
MEDICAL CENTER

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

MICHAEL S. BROWN, M.D.

REGENTAL PROFESSOR

DIRECTOR OF THE JONSSON CENTER FOR MOLECULAR GENETICS UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS

NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE, 1985

MEMBER, NATIONAL ACADEMY OF SCIENCES

Michael S. Brown received an M.D. degree in 1966 from the University of Pennsylvania. He was an intern and resident at the Massachusetts General Hospital, and a post doctoral fellow with Earl Stadtman at the National Institutes of Health. He is currently Paul J. Thomas Professor of Molecular Genetics and Director of the Jonsson Center for Molecular Genetics at the University of Texas Southwestern Medical School in Dallas. Dr. Brown and his colleague, Dr. Joseph L. Goldstein, discovered the low density lipoprotein (LDL) receptor, which controls cholesterol in blood and in cells. They showed that mutations in this receptor cause Familial Hypercholesterolemia, a disorder that leads to premature heart attacks. Their work laid the groundwork for drugs called statins that block cholesterol synthesis, increase LDL receptors, lower blood cholesterol and prevent heart attacks. Statins are taken daily by more than 20 million people worldwide. Brown and Goldstein shared many awards for this work, including the U.S. National Medal of Science and the Nobel Prize for Medicine or Physiology.

SCAP: ANATOMY OF A MEMBRANE STEROL SENSOR

Scientists have learned much about the complex lipid composition of membranes, but we know little about how these lipids are regulated. Our laboratory has made progress in understanding the control of one membrane lipid: cholesterol. Precise control of membrane cholesterol is essential because too little cholesterol is lethal through defective membrane function. Too much cholesterol is lethal through formation of toxic cholesterol crystals. The job of adjusting membrane cholesterol falls on Scap, a polytopic membrane protein of the endoplasmic reticulum (ER). Scap transports transcription factors called Sterol Regulatory Element Binding Proteins (SREBPs) from the ER to the Golgi where they are processed to release a nuclear fragment that activates the genes necessary to synthesize cholesterol. When excess cholesterol accumulates in the ER it binds to Scap and blocks movement to the Golgi. Transcription of the cholesterol-synthesizing genes declines and cholesterol balance is restored. Scap is a complex protein with eight transmembrane helices, three large hydrophilic loops and a 500 residue COOH-terminal extension. We have identified four separate domains that mediate ER-to-Golgi transport, cholesterol binding, cholesterol-dependent ER retention, and SREBP binding. These studies reveal a fundamental mechanism by which cells control the lipid content of membranes.