



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)
Michael S. Brown (2013)



EARL W. SUTHERLAND LECTURE

SPONSORED BY:
DEPARTMENT OF MOLECULAR PHYSIOLOGY AND BIOPHYSICS

ROBERT J. LEFKOWITZ, MD

NOBEL PRIZE IN CHEMISTRY, 2012

SEVEN TRANSMEMBRANE RECEPTORS

MARCH 31, 2016

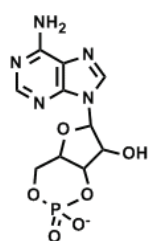
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208 LIGHT HALL

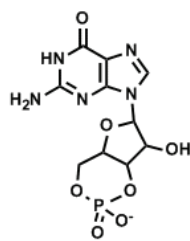
VANDERBILT  UNIVERSITY
MEDICAL CENTER

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



cAMP



cGMP

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.



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MEMBER, INSTITUTE OF MEDICINE

NOBEL PRIZE IN CHEMISTRY, 2012

Robert J. Lefkowitz, MD is James B. Duke Professor of Medicine and Professor of Biochemistry and Chemistry at the Duke University Medical Center. He has been an Investigator of the Howard Hughes Medical Institute since 1976. Dr. Lefkowitz began his research career in the late 1960’s and early 1970’s, when there was no clear consensus that receptors even existed. His group spent 15 years developing techniques for radioligand binding, solubilization, purification, and reconstitution of the four adrenergic receptors known at the time. In 1986, Dr. Lefkowitz transformed the understanding of what had become known as G protein coupled receptors (GPCRs), when he and his colleagues cloned the gene and cDNA for the β_2 adrenergic receptor, and recognized its sequence homology with rhodopsin, thus establishing them as the first members of a new family of proteins, the Seven Transmembrane Receptors (7TMRs). This superfamily is now known to be the largest, most diverse, and most therapeutically accessible. Since then, Dr. Lefkowitz has continued to revolutionize the GPCR field through discovery and cloning of the G protein coupled receptor kinases (GRKs) and β -arrestins; and discovery of “biased” signaling through β -arrestins or G proteins. Most recently, he has been applying the tools of structural biology to understand biased signaling at atomic level resolution. He has received numerous awards and honors, including the National Medal of Science, the Shaw Prize, the Albany Prize, and the 2012 Nobel Prize in Chemistry. He was elected to the USA National Academy of Sciences in 1988, the Institute of Medicine in 1994, and the American Academy of Arts and Sciences in 1988.

SEVEN TRANSMEMBRANE RECEPTORS

Seven transmembrane receptors (7TMRs), also known as G protein coupled receptors (GPCRs) represent by far the largest, most versatile, and most ubiquitous of the several families of plasma membrane receptors. They regulate virtually all known physiological processes in humans. As recently as 40 years ago, the very existence of cellular receptors for drugs and hormones was highly controversial, and there was essentially no direct means of studying these putative molecules. Today, the family of GPCRs is known to number approximately 1,000, and crystal structures have recently been solved of approximately 25 members of the family and even of a receptor-G protein complex. In my lecture, I will briefly review how the field has evolved over the past 40 years, hanging some of the story on my own research throughout this period. Then I will discuss recent developments in the field, which are changing our concepts of how the receptors function and are regulated in fundamental ways. These include the duality of signaling through G-proteins and β -arrestins; the development of “biased ligands”; and the possibility of leveraging this new mechanistic and molecular information to develop new classes of therapeutic agents. Finally, I will discuss recent biophysical and structural studies of receptor-barrestin interactions.