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Robert J. Lefkowitz and Discovery of the G-Protein-Coupled Receptor Family

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Biography

Robert J. Lefkowitz is a professor at the Duke University of Medicine, where he also leads the Lefkowitz lab. He is known for his research contributions in the study of G-protein-coupled receptors. He received the Nobel Prize in Chemistry in 2012 along with one of his fellow researchers, Brian Kobilka, for their "studies of G-protein-coupled receptors" (Linse, 3).

Personal

Robert J. Lefkowitz was born on April 15, 1943 in New York, NY ("Robert J. Lefkowitz – Facts"). Lefkowitz wanted to become a physician because he greatly admired his family doctor, Dr. Feibush (Snyderman 4193). He has five children with his first wife, Arna Gornstein. He has been married to Lynn Tilley Lefkowitz since 1991. ("Robert J. Lefkowitz – Biographical").

Education

- Bachelor of Arts in Chemistry, 1962, Columbia University ("Lefkowitz Bio").
- Doctor of Medicine, 1966, Columbia University ("Lefkowitz Bio").

Awards

Lefkowitz has received many awards throughout his career, including ("Lefkowitz Bio"):

- The Association of America Medical Colleges' Biomedical Research Award (1990)
- The National Academy of Sciences' Jessie Stevenson Kovalenko Medal (2001)
- The Shaw Prize in Life Science and Medicine (2007)
- National Medal of Science (2007)
- Nobel Prize in Chemistry (2012)

Left: Nobel Chemistry Prize ("The Nobel Prize in Chemistry").
Right: National Medal of Science ("President Obama honors").

Professional Experience

Lefkowitz began his residency in internal medicine at Columbia University in 1967 ("Robert J. Lefkowitz – Bio"). From 1968 to 1970, Lefkowitz joined the commissioned served as Clinical and Research Associate at the National Institutes of Health (NIH) ("Robert J. Lefkowitz – Biographical"). After his time at NIH, he did an additional year of an internal medicine residency and two years of a cardiology fellowship at Massachusetts General Hospital (MGH) ("Robert J. Lefkowitz – Biographical"). In 1973, Lefkowitz was hired as an Associate Professor of Medicine at Duke University ("Robert J. Lefkowitz – Biographical"). He has continued to teach at Duke as a professor of medicine, biochemistry, chemistry, and pathology while also working at the Howard Hughes Medical Institute as an Investigator since 1976 ("Robert J. Lefkowitz – Bio"; "Robert J. Lefkowitz – Biographical"). He began his career with a blend of clinical and laboratory responsibilities, but he has not engaged in clinical work for over ten years ("Robert J. Lefkowitz – Biographical").

Lefkowitz's Research

In his paper, "Cloning of the gene and cDNA for mammalian β-adrenergic receptor and homology with rhodopsin," Lefkowitz and his fellow researchers revealed how they successfully cloned and sequenced the βAR gene. As a result of this work, Lefkowitz and others made the significant discovery that "[t]he sequence homology between βAR and rhodopsin parallels similarities in their function," which led to the belief that other G-protein-coupled receptors (GPCRs) would share these structure similarities (Lefkowitz et al., "Cloning" 78; Lefkowitz, "Historical Review" 416).

GPCRs are proteins in the plasma membrane that allow for the transmission of information from outside of the cell to the inside (Linse 1). Every human cell is enclosed by a plasma membrane, which allows the cell to "maintain a specific mix of biochemically active species" while blocking other substances from the outside (Linse 1). GPCRs mediate a wide array of physiological signals, such as a change in hormones, from outside the cell and communicate these changes to the inside of the cell (Linse 2). This information will then cause reactions involving other proteins to deliver the "appropriate cellular and physiological response" (Linse 2).

The advances in microsequencing techniques allowed for "the cloning of the gene and cDNA encoding the hamster β_2-adrenoceptor" (Lefkowitz, "Historical Review" 415). Because cDNA clones were scarce and most cDNA libraries had limited independent recombinants, cloning was a difficult process, but Brian Kobilka, the other recipient of the 2012 Nobel Prize for Chemistry, successfully constructed a genomic library that allowed for Lefkowitz and his team to make the seminal discovery of the GPCR family (Lefkowitz, "Historical Review" 416). Since the β_2-adrenoceptor was intronless, "the clones quickly yielded the entire deduced amino acid sequence of the receptor from a single exon" (Lefkowitz, "Historical Review" 416).

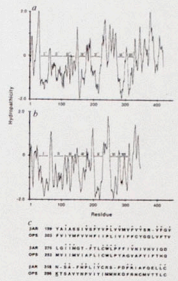


Figure 1. The similarities between the graphs of the hydropathicity profiles of hamster βAR (Graph a) and bovine opsin (Graph b) demonstrate the structure and sequence homology of the two proteins. The amino-acid sequence homologies between the hamster βAR and bovine opsin are also demonstrated (Graph c) (Lefkowitz et al., "Cloning" 78).

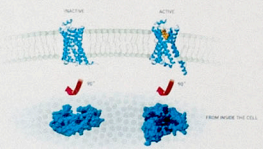
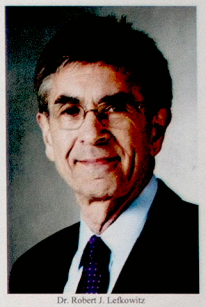


Figure 2. The βAR gene was the receptor that was examined in Lefkowitz's 1986 study. On the top left, an inactive βAR is shown, while the βAR that has been activated after bounding to ligand (orange object) and G-protein is on the top right. The bottom two images show the view of the receptors from inside the cell membrane (Linse 2).



Dr. Robert J. Lefkowitz
("Robert J. Lefkowitz – Biographical").

Biochemistry

Lefkowitz made his research contributions in the field of biochemistry. According to the American Chemical Society, biochemistry is "the study of the structure, composition, and chemical reactions of substances in living systems" ("Biological/Biochemistry"). Although biochemistry has become its own discipline, it requires techniques from other related fields such as analytic, organic, and physical chemistry in order to study the chemistry of life (Vennesland and Stotz).

Similar to how biochemistry draws on skills from other related fields, it has applications in numerous industries. For example, biochemists at a company such as Dow Agrosciences may study how a potential active ingredient in an herbicide could affect soybean yields. Biochemistry also plays a key role in fields such as pharmacology and microbiology ("Biological/Biochemistry"). Lefkowitz's biochemistry research has had a major impact on pharmacology and microbiology.

Impact of Lefkowitz's work

Lefkowitz's discovery of the large family of GPCRs has had a significant impact on the practice of medicine, as "[t]heir central importance and relevance to the current clinical practice of medicine is reflected in the plethora of drugs that target these receptors" (Lefkowitz, "Historical Review" 413). Medications such as selective serotonin reuptake inhibitors (SSRI) either directly or indirectly target the GPCRs (Lefkowitz, "Historical Review" 413). Furthermore, Lefkowitz paved the way for subsequent studies of GPCRs, and other researchers have found that "there are ~1000 genes encoding [GPCRs] in the human genome, and these receptors regulate virtually all known physiological processes in mammals" (Lefkowitz, "Historical Review" 413). Prior to Lefkowitz's research, even the existence of such receptors was questioned. Raymond Ahlquist, the prominent pharmacologist who developed the concept of distinct α- and β-adrenoceptors, stated that the receptors were "an abstract concept" (Lefkowitz, "Historical Review" 413).

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