2011 Association of American Physicians George M. Kober Medal

Introduction of Robert J. Lefkowitz

Ralph Snyderman

At the 1924 meeting of the Association of American Physicians, the George M. Kober Medal was established to honor AAP members who have distinguished themselves through contributions to medicine. There is no greater honor that can be bestowed by the AAP on one of its members.

Today, we honor one of the true greats of contemporary medicine and biomedical research — Dr. Robert J. Lefkowitz. In thinking about how one defines the greatness of an individual's achievement, I find it interesting and ironic that one can quantify greatness as an inverse relationship with the number of words it takes to describe it. For example, Newton — gravity; Darwin — evolution; Einstein — relativity; Lefkowitz — *receptaz*. Notice it's *receptaz*, not receptors. The importance of this distinction will become apparent as I tell you about Bob Lefkowitz's life.

To better appreciate Bob's contributions to our understanding of receptor function, it's useful to compare what we now take for granted with where we were when he started. Today, all medical students are taught about the broad field of G protein–coupled receptors being seven membrane-spanning proteins on cell surfaces that mediate cellular responses to hormones, neurotransmitters, odorants, chemokines, and taste. They are taught about the structure-function and detailed regulation of these receptors, as well as the drugs that stimulate or inhibit them. This knowledge is almost taken for granted, and much is a consequence of Bob's work.

When Bob began his research in 1968, receptors were postulated to account for downstream effector function; but Ahlquist, who had developed the concept of distinct α- and β-adrenoreceptors, wrote in 1973, "they were an abstract concept conceived to explain observed responses of tissues produced by chemicals of various structures" (1). Even Sutherland, who received the Nobel Prize for the discovery of adenylate cyclase (Figure 1), posited that "the β-receptor and adenylate cyclase are the same" (2).

Since starting at the NIH with Jesse Roth and Ira Pastan, and throughout his career, Bob created a trail of ever more detailed research findings that has given us an in-depth understanding of what receptors are and how they work. Bob has uncovered this knowledge through asking important questions that require technical breakthroughs to answer, thereby enabling a deeper understanding of receptors, but leading to even more interesting questions requiring new technical capabilities. Through this process, Bob and his coworkers have led us to much of our current understanding of GPCRs.

For his remarkable body of work, Bob has been widely recognized with more than 60 important awards, of which 10 are represented here (Table 1). But research is only one part of Bob's contributions. Through his mentorship, he's trained over 200 outstanding investigators, dozens of whom are legends in their chosen field of research and many who are members of AAP (Table 2). Bob has also led in organizations such as the National Academy of Sciences, the ASCI, the AAP, and at Duke, where, he will eagerly attest, I served under his direction as chancellor for 15 years.

So what is the essence of Bob that led to these accomplishments? It is hard to imagine how one individual could have possibly achieved so much while being so genuinely loved and admired by his colleagues. In being asked to present this award, I considered it to be a fascinating opportunity to learn about what it took to bring Bob to where he is now. Even though I've known him for almost 40 years, have run over 60,000 miles with him (Figure 2), and consider him to be my closest friend, I took this assignment as an opportunity to understand not only what he did, but how he developed to be this year's Kober Medalist.

Bob's grandparents were born in Poland and migrated to the United States in the latter part of the 19th century. Bob's parents were Max and Rose Lefkowitz. Max grew up in a family with six siblings and lived in the lower east side of Manhattan (Figure 3A). He went to Brooklyn College, where he received a degree in accounting, then worked in the garment district of Manhattan. Rose was born in New York City and grew up in Manhat-

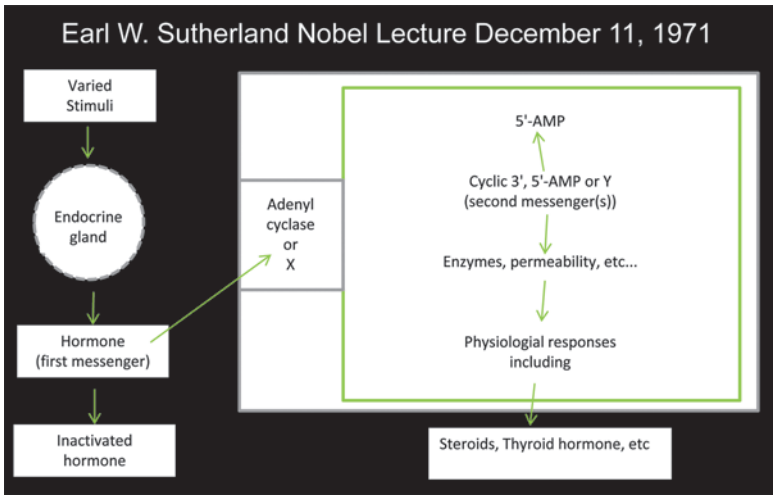

Figure 1
Putative role of adenylate cyclase alone or with a receptor in activating cellular responses to hormones.

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Table 1
Awards received by Robert J. Lefkowitz

Gairdner Foundation International Award
American Heart Association Basic Research Prize
Bristol-Myers Squibb Award for Distinguished Achievement in Cardiovascular Research
Jessie Stevenson Kovalenko Medal, The National Academy of Sciences
Institut de France Fondation Lefoulon-Delalande Grand Prix for Science
Albany Medical Center Prize in Medicine & Biomedical Research
The Shaw Prize in Life Science and Medicine
National Medal of Science
Research Achievement Award, American Heart Association
BBVA Foundation Frontiers of Knowledge Award

Table 2
Trainees of Robert J. Lefkowitz

R. Wayne Alexander	Stephen Liggett	Linda Pike
Jeffrey Benovic	Lee Limbird	John Raymond
Michel Bouvier	Martin Lohse	Debra Schwinn
Marc Caron	Jon Lomasney	David Sibley
Richard Cerione	Louis Luttrell	Gary Stiles
Susanna Cotecchia	Frederico Mayor	Catherine Strader
Andre de Lean	Thomas Michel	Warren Strittmatter
Henrik Dohlman	Carmelo Milano	Ron Vale
Brian Hoffman	Kurt Newman	Michael Wessels
James Inglese	Lina Obeid	Lewis Williams
Brian Kobilka	Brian O'Dowd	R. Sanders Williams
Walter Koch	Gang Pei	

tan. Max and Rose were married in 1937 (Figure 3B), and Robert J. Lefkowitz was born on April 15, 1943, in the Bronx (Figure 3C). He grew up in Parkchester, a vast development of apartment houses in the Bronx (Figure 3D). Bob's early childhood experiences were very positive, where as an only child he was treated like a king (Figure 3E). He lived in a two-bedroom, one-bath apartment on the sixth floor of a seven-story apartment house next to the elevator. As a child, he entertained himself through his voracious appetite for reading his parents' books.

Bob's father, Max, who Bob truly loved and admired, was quiet, unassuming, loving, and would do anything for Bob. He was always there for him. While gifted intellectually, Bob was by no means an inheritor of great athletic prowess. In gym class, it was necessary to tumble and climb a rope to the ceiling of the gym, and Bob was able to do neither. Learning of this, his father worked with him so that he could tumble over stacked pillows in their living room. To be able to climb the gym rope, his father constructed a rope in their apartment, obviously not a very high one, allowing Bob to learn how to twist the rope around his leg and climb to the top. He was thus able to achieve what was required from him in his gym class.

Bob's mother, on the other hand, was incredibly demanding. She expected excellence and would accept nothing less. When Bob would write an essay, scribbling on a pad with his pencil and overly using the eraser, his mother would insist that he keep rewriting his essay until it was absolutely perfect. She was equally unyielding if Bob's grades were anything other than perfect. Nonetheless, she could also be supportive. When Bob and his friends were caught stopping elevators between floors in their apartments, the guard reprimanded Bob and told him that he was going to take his name, which he did. Bob ran home hysterically, thinking his name was no longer his. He told this to his mother, who comforted him and said, "He didn't actually take your name, Bob; he wrote down your name. Your name is still Bob Lefkowitz." So, at this point, do we have any hint that Bob was on a trajectory that would lead him to receiving the Kober Medal today?

Bob's ambition early on, like so many kids in the Bronx, was to become a professional baseball player like Mickey Mantle (Figure 4A). However, his lack of agility and coordination, his poor vision, and minimal skills in stickball conspired to predict that he would not succeed in that occupation. Thus, by the third grade, Bob decided that the career of a physician was for him in part because he idolized Dr. Feibush, their family doctor.

A pivotal moment in Bob's life occurred at about the age of 7 when he was being forced to take piano lessons (Figure 4B). Bob's mother felt that he should have competence in playing the piano and, despite the small size of their apartment, made sure they had an upright for him to practice on. Bob was to practice an hour each day, an activity he hated. This being the case, he would always schedule his practice hour shortly before his mother was to do grocery shopping. Being clever even at this age, he would wait for her to go out the apartment door, listen carefully for the arrival, then the departure of the elevator, which, as you know, was right next to their apartment. Then, knowing that his mother was gone, he would go out and play with his friends. One day, being particularly motivated to play outdoors, Bob started his piano lesson about five minutes before his mother was to leave. Then when she did, he listened carefully for the elevator to arrive to his floor and then depart.

On this particular day, Bob was even more cautious and waited an additional five minutes to be sure that his mother was gone, and then to be even more certain, he walked to the apartment door peephole to make sure that she wasn't still there. When Bob opened the peephole, what did he see but his mother's eye staring right back at him and immediately

Figure 2
Bob (left) and Ralph Snyderman (right) beginning a 10K run.

Figure 3
Bob's grandparents and parents; Bob as a child. (**A**) Max Lefkowitz (top row, second from left) with siblings and parents. (**B**) Bob's parents, Max and Rose Lefkowitz. (**C**) Birth announcement of Robert Joseph Lefkowitz. (**D**) Bob with father, Max, and mother, Rose. (**E**) "King Bob" at 18 months.

heard her voice — "Bobby, I knew you were up to no good!" This experience had a profound effect on Bob's life and in my view, his mother's eye, and all that it represents, is constantly overseeing and recognizing any of his activities that are less than perfect — a standard that continues to drive Bob through this very moment when he is rehearsing his remarks, which will follow mine.

Bob went to the elementary school PS102, within walking distance of his apartment. In junior high, Bob's most profound recollection was that for the first time he discovered girls, although he did nothing about it (Figure 5A). Bob worked hard to get into the Bronx High School of Science where he encountered the toughest peer group competition he ever faced and he and his classmate, David Botstein, graduated with GPAs of 94.

Bob chose Columbia for his undergraduate education because he was then going steady with Arna, his childhood sweetheart, and Colombia accepted him with an early decision and a scholarship. He was recognized by himself and others as a first-class geek and he graduated in three years at the age of 19. Upon graduation, he became engaged to Arna.

For medical school, Bob chose Columbia and as yet had no particular interest in pursuing a career in research. When he had the opportunity to take research electives, he chose to take sub-internships instead. Bob was, however, influenced by two academic physicians — Paul Marks and Dickerson Richards, from whom he learned that science was the backbone of clinical medicine. His close friend in medical school was Harold Varmus.

Bob married Arna during his first year of medical school and by his second year was the father of David and one year later Noah. Bob continued to be a consummate geek and on clinical rounds, he was a terror. He enjoyed memorizing obscure and unimportant facts and then deploying them strategically with the attending to the dismay of his classmates. It is not surprising that Bob graduated at the top of his class (Figure 5B). Bob decided to be a cardiologist in part because his father, who Bob loved dearly, had his first heart attack in 1955.

Bob selected Physicians and Surgeons (P&S) for his internship and residency, and, as this was during the height of the Vietnam War, he applied to the National Institutes of Health for a clinical associate position and a commission in the Public Health Service. He matched in the laboratory of Jesse Roth and Ira Pastan at NIAMD. In recounting Bob's interview, Jesse recalls him as having a bushy crewcut and horned-rimmed glasses, with Bob trying unsuccessfully to convince Jesse that he truly was interested in research. Jesse correctly assumed that Bob was more commit-

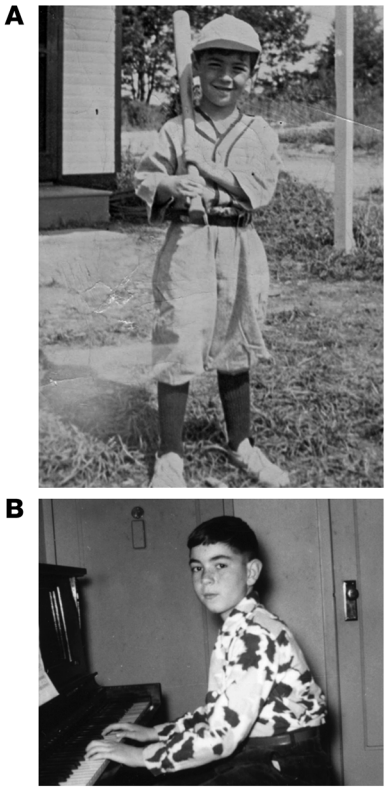

Figure 4
Bob ready for baseball and practicing the piano. (**A**) Note that the bat is being held incorrectly for a "righty." (**B**) Note the keyhole on the front door to the left of Bob.

ted to making his flight back to New York to start his internship. Nonetheless, based on Bob's stellar academic accomplishments rather than the interview, Jesse kept Bob on his list and Bob matched in his lab.

Bob completed his first two years of house staff training and on the morning of July 1, 1968, he and Arna and their three kids piled into their Dodge Dart and drove to Rockville. Bob's vision as a clinical associate was to become the consummate physician-attending in a prestigious academic teaching hospital, and when he began, he viewed this experience as a potential of checking off the box of having done laboratory research.

Jesse Roth was an established but young investigator, had one technician, and generally two fellows, of which Bob was one. Bob, like so many of us, was given a bench and a module and was off on his own. At that time, receptors had not definitively been shown to be physical structures. Jesse and Ira felt that to validate the existence of receptors, it would be important to develop a biologically relevant direct ligand-binding assay. Bob's research was to take homogenates of an adrenocortical carcinoma and using radioiodinated ACTH show specific binding was associated with activation of adenylate cyclase. To do this, Bob was to iodinate ACTH, separate iodinated from unlabeled ACTH, and show that the iodinated ACTH used for binding retained biological activity, a difficult task at that time. As Bob immersed himself in his first major biomedical research experience, what was his feeling? Virtually total disgust, because nothing worked! Jesse indicated that Bob needed two hourly pep talks per week just to keep him going. In a conversation Bob had with his father on Thanksgiving of his first year at the NIH, they both decided that Bob shouldn't fret too much about his lack of success in the laboratory, as he really wanted to be an academic physician and not a researcher. Bob's father had his fourth and fatal heart attack on December 17 of that year and, at least on earth, never learned of Bob's subsequent successes and joy as a researcher. Nonetheless, he was comfortable that Bob had a plan and would be pursuing a career in academic medicine.

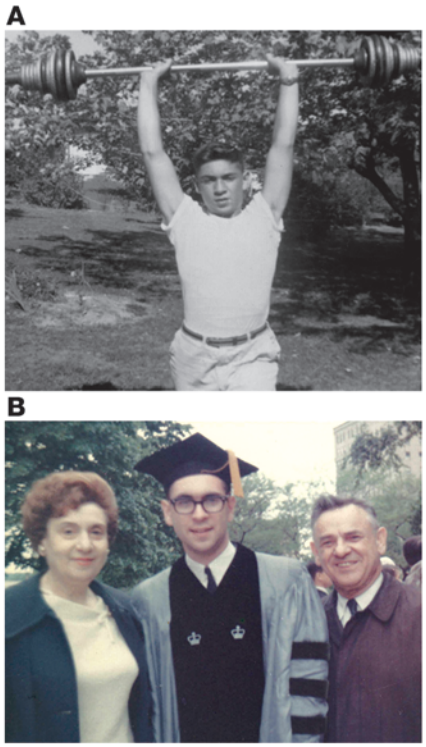

Figure 5
Teenage Bob and medical school graduation. (**A**) Muscular Bob. (**B**) Bob and his parents.

Approximately 14 months after Bob began his research, he finally got iodinated ACTH to specifically bind to the cancer membranes and stimulate adenylate cyclase. By 1970, Bob had a major publication in *PNAS* (3) and a second publication in *Science* (4). He was now very enthusiastic about biomedical research, but as he had applied and was accepted to the MGH for a senior residency, followed by a cardiology fellowship in Ed Haber's division, he felt obligated to take a side step from his career as a researcher.

When Bob began his cardiology research project, his research interests were toward physiological approaches. He was told by Ed Haber to speak with Charlie Sanders, who was head of the cath lab. That discussion turned out to be a major turning point for Bob. Charlie told him that researchers in cardiac physiology were "a dime a dozen" and that Bob should stick to his molecular work where he could forge a whole new field.

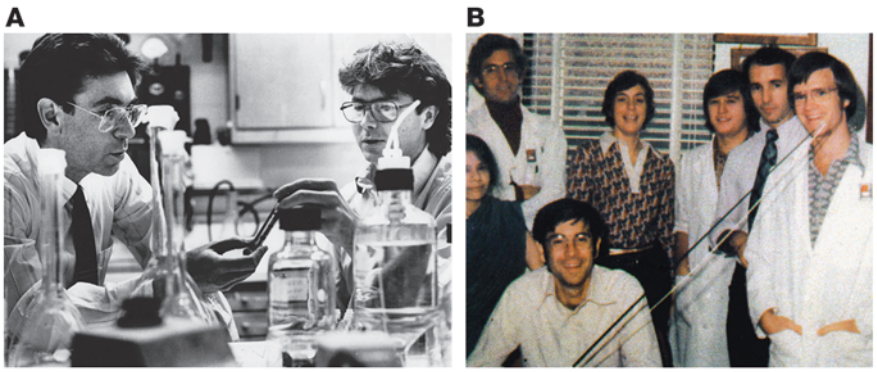

Figure 6
Bob with his lab members. (**A**) Bob in the lab with John Reagan. (**B**) Chobi Mukherjee, John Mickey, Lee Limbird, Marc Caron, Wayne Alexander, and Rusty Williams.

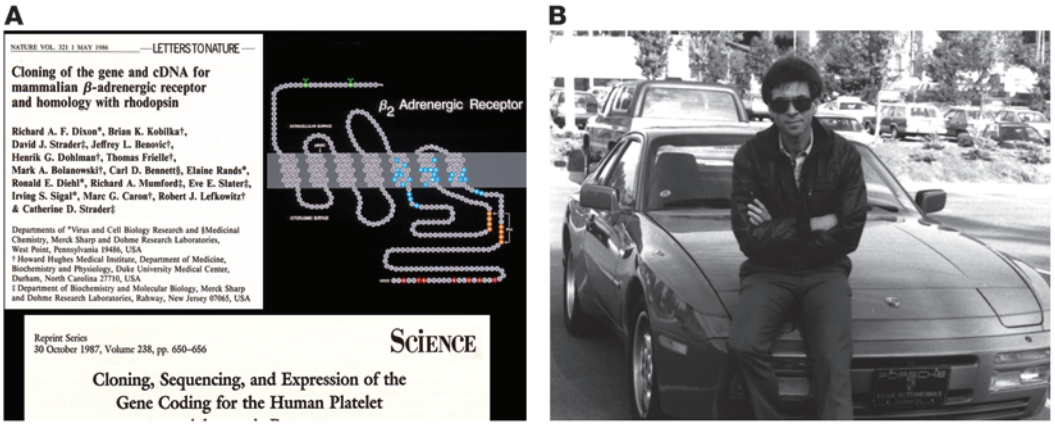

Figure 7
Seminal manuscripts and Bob's reward. (**A**) Manuscripts describing original cloning, sequencing, and structure of the β-adrenergic receptor. (**B**) Bob's reward — a 1986 Porsche 944T.

Bob followed this advice and joined Ed Haber's laboratory for his research project. With Bob's background in radiolabeling, Ed tried hard to get him to work on a binding assay for the aldosterone receptor. At this point, Bob demonstrated a key characteristic that shaped the rest of his career — a dogged determination to pursue the research areas that he found most interesting and important. Bob was interested in adenylate cyclase–coupled receptors, so he turned Ed down. Bob's initial choice was the glucagon receptor, but as there were no variants of glucagon for structure-function relationships, he switched to the β-adrenergic receptor as a model and did so following a great deal of literature investigation and planning.

I believe at this point, Bob "got his legs" as an independent investigator and, in retrospect, made exactly the right choice. With this receptor, Bob's work had a model with cardiovascular relevance and a plethora of agonists and antagonists. While a cardiology fellow, Bob worked on developing a tritiated norepinephrine-binding assay for β-receptors on myocardial membranes (5). Through his presentations at the American Heart Association and clinical meetings, he caught the attention of Andy Wallace and Jim Wyngaarden at Duke, both of whom were in their golden eras of recruiting promising young faculty to Durham. Bob visited Duke in the summer of 1972 and came away feeling that he was in no way interested in coming to that institution. Nonetheless, he received a letter from Jim Wyngaarden with a firm offer for a faculty position as an assistant professor. Bob's alternative was to become a chief resident at the MGH with Alexander Leaf and, a year later, join the MGH as an assistant professor. After Bob turned down Jim Wyngaarden's offer, he received a call from Andy Wallace indicating that he and Jim Wyngaarden rejected Bob's rejection and would appreciate him coming up with the offer that would bring him to Duke. As Bob didn't want to go, he wrote a letter asking for what he thought were outrageous conditions that he was sure would squelch the recruiting efforts. To his surprise, Bob got a call from Andy Wallace indicating that he would be getting an offer letter that gave him everything he

Figure 8
Bob and Lynn's wedding.

Figure 9
Bob is pleased with his research.

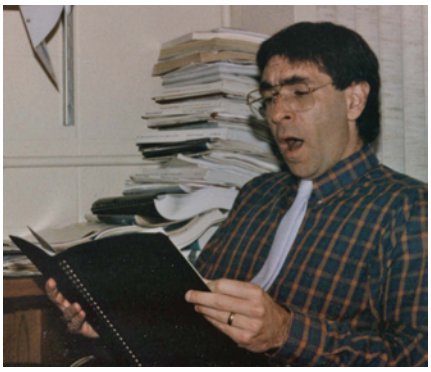

Figure 10
Bob having a "eureka" moment.

asked for, including a position of associate professor with tenure and a salary far greater than Bob ever imagined.

In July of 1973, Bob and family again packed all their belongings and moved to Durham, North Carolina, where Bob occupied spanking new laboratories and offices on the third floor of Sands Building, with my laboratory on the adjacent hall (Figure 6A). As Bob got started, he took on three fellows, all of whom not only did groundbreaking work with Bob, but all of whom became tremendously successful in their own right. First was Marc Caron, second was Lee Limbird, and the third was a literal spur-of-the-moment walk-in — Rusty Williams (Figure 6B).

The initial work in Bob's lab at Duke focused on developing more effective binding assays for β-adrenergic receptors, and by spring 1974, they had extremely effective assays (6, 7). In the fall of 1974, Bob, Marc, Lee, and Rusty outlined a research plan that laid out the direction of the Lefkowitz laboratory, which continued to the era of cloning in the mid-'80s.

Here begins the incredible journey by Bob and his colleagues. Through their development of functional binding assays in cellular membranes, Bob and colleagues demonstrated a multiplicity of adrenergic receptors and their subtypes and demonstrated that receptors became desensitized upon agonist exposure. Through highly refined ligand-binding analysis, they demonstrated different radioligand competition curves with agonists versus antagonists and showed that binding was modifiable by GTP. This allowed the development of the ternary complex model of receptor interacting with a GTP-binding G protein to form a high-affinity receptor–G protein complex that activates adenylate cyclase (8, 9).

The purification and the complete reconstitution of receptor, G protein, and adenylate cyclase in vesicles conclusively validated the ternary complex model as well as the functional nature of the isolated receptors (10, 11). Through the technologies they developed for receptor purification using affinity chromatography matrices, they demonstrated that the desensitized receptor was phosphorylated, not only by PKA, but by a novel kinase which they initially called the β-adrenergic receptor kinase (BARK), which they purified, cloned, and found to be functionally similar to the enzyme rhodopsin kinase (12–15).

In 1984, Bob began a collaboration with investigators at Merck to clone the β_2 adrenergic receptor based on the availability of short stretches of protein sequence from work in Bob's lab. They were unsuccessful for two years when Brian Kobilka, then a fellow in Bob's lab, wanted to learn cloning. After four one-week trips to Merck, Brian initiated cloning efforts in Bob's lab. When repeated attempts at cDNA cloning failed, Brian made the bold, and some thought harebrained, decision to clone the β-receptor through a genomic approach. From a size-selected genomic library he created, they soon cloned the β_2-adrenergic receptor. The sequencing of this receptor allowed Bob and colleagues to determine that this receptor was similar to rhodopsin, the only other seven membrane-spanning receptor whose sequence was known at the time (Figure 7A and ref. 16). As the β_2 receptor and rhodopsin had similar features, weak sequence homology, and both were known GPCRs, Bob and colleagues immediately proposed that the entire broad family of GPCRs would all be seven membrane-spanning proteins (17). In 1986, the β_2 receptor was cloned, BARK was discovered, and all the work laid out in the 1974 plan was largely completed. A whole new horizon could be envisioned.

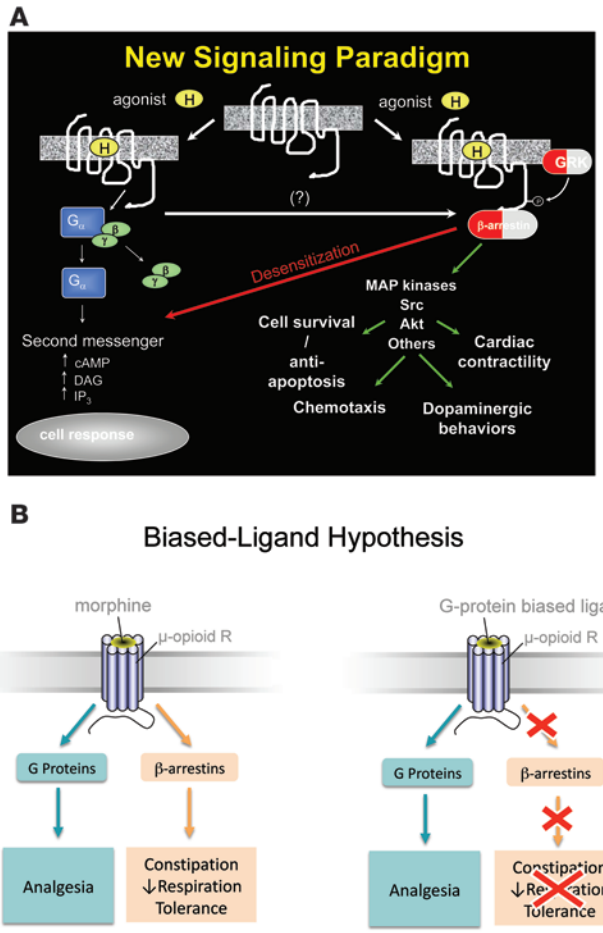

Figure 11
Dual signaling pathways and biased-ligand hypothesis. Dual signaling pathways of GPCRs (**A**) give rise to the concept of biased ligands as more effective therapeutics (**B**).

Figure 12
Bob receiving the National Medal of Science from President George Bush.

A major piece of the receptor regulation puzzle was solved through the identification of β-arrestin. Using reconstitution systems to study desensitization, Bob found that as the BARK protein was sequentially purified, it became less and less active, indicating that something necessary for desensitization was lost in the purification. He soon came across a manuscript describing S-antigen, later renamed arrestin, which was related to the function of rhodopsin kinase. Bob secured some of the highly purified arrestin and in his reconstitution assay found that it indeed reconstituted the desensitizing ability of BARK, but the efficiency was very low. Shortly thereafter, the retinal arrestin protein was cloned, and using its sequence, Bob's lab was able to clone the new proteins β-arrestin1 and β-arrestin2, where, in reconstitution experiments, the specificity of arrestin and β-arrestins respectively for rhodopsin versus adrenergic receptor matched perfectly (18–20).

Importantly, in 1991, Bob married Lynn Tilley Lefkowitz, his dearest love and partner, who is with him today (Figure 8). By the early 1990s, Bob and his colleagues had cloned eight adrenergic receptors, a serotonin receptor as well as multiple G protein–coupled receptor kinases, and β-arrestin1 and -2 (Figure 9).

The ability to use these tools allowed Bob's parallel pathways of research on receptor structure, function, and desensitization, to come together. Through the use of receptor mutagenesis and the construction of the first chimeric receptors, Bob and colleagues elucidated much of what is currently known about the structure function relationships of GPCRs and defined the precise mechanisms of receptor desensitization. A major observation from these studies was that β-arrestin, in addition to its role in receptor desensitization, was involved in receptor endocytosis and activation of ERK and other MAP kinases (21–23). This led to the understanding that GPCRs utilize two major signaling mechanisms — one is mediated through the classical activation of G proteins and the other through the activation of β-arrestins (24, 25). The observation that GPCRs signal through G protein and β-arrestin pathways has profound implications for not only the understanding of cell biology but also for drug development.

In 2004, Bob was in his study at home at about 10 pm reading a manuscript (Figure 10) when he learned about an angiotensin receptor agonist that stimulated receptor internalization but not activation of G protein signaling. In what Bob described as a mini-eureka, he hypothesized that this

Figure 13
Bob with his children and grandchildren. (**A**) Bob and his children — Josh, Noah, David, Cheryl, and Mara. (**B**–**C**) Bob and his grandchildren — Jonah and Maya (**B**); Maddie and Samantha (**C**).

Figure 14
Bob in his office waiting for data.

might be an indication of exclusive activation of the β-arrestin pathway, implying that a ligand might be "biased" toward activating only one pathway. By the next day, he had already called the investigators and secured all 12 of their ligands to the angiotensin receptor and soon demonstrated the ability of several of them to selectively activate the β-arrestin versus the G protein pathway (26).

These findings bring us to Bob's current focus of research (Figure 11A), understanding even more deeply the receptor conformations necessary for the mediation of G protein versus β-arrestin signals and uncovering the consequences of dual signaling and the biased ligand hypothesis (27, 28). Based on Bob's work, Trevena, a company founded by Bob and Howard Rockman, is currently pursuing the development of drugs with bias to important GPCRs, thereby selecting desired activities and minimizing adverse side effect (Figure 11B).

His recent contributions have not gone unnoticed and in 2008, he was awarded the National Medal of Science by President George Bush (Figure 12). Even more importantly for Bob is his dear family — 5 children, 4 grandchildren, and his wife Lynn (Figure 13).

So, how do we put this all together to understand how Bob Lefkowitz came to be who he is and to do all he has done? You've seen the component parts. Starting with roots in Poland to Rose and Max Lefkowitz in the Bronx in 1943, Bob's inheritance and upbringing somehow created the individual we now know. His father's gentle, supportive caring and love contributed to Bob's confidence; his mother's demand for excellence, hard work, the all-seeing eye, the intense competition from his peer generation of recent immigrants to the US, his drive and focus on being the best, the outstanding training opportunities available, including the experience at the NIH brought about by the Vietnam War, and beginning research when big questions could be envisioned and new technologies were emerging gave him vast opportunities — all these components are part of the story. But many individuals had similar opportunities, yet only one became Bob Lefkowitz. While we can never understand the mystery of what makes people who and what they are, we can describe traits they inherit and develop that enable that individual to respond to the vagaries of circumstances and get them where they are. In Bob, they are:

1. Extremely high intelligence.
2. An insatiable desire to attain perfection.
3. An incredibly hard work ethic.
4. Exquisitely high standards and expectations for his performance.
5. Persistence toward obtaining his goals.
6. An unswerving focus on the things he feels are important and the avoidance of things that are distractions.
7. A strong intuitive sense of what should or should not be done.
8. An incredible amount of courage and persistence despite difficulties and failures.

Along with these are additional critical characteristics:

1. A sense that what he is doing is very important, monumental.
2. A feeling of optimism, at least as it relates to his research; a feeling that the difficult things he wants to do can be done.
3. Insatiable curiosity, wanting to understand complex biological processes and absolutely loving to analyze data. I well recall a time when my office needed to be moved to his hall, since renovations were occurring in mine. What was remarkable, coming from Bob's hallway, was a din of continual shrieks of joy and excitement and interactions amongst the researchers with Bob's voice drowning out all the others coming from his office saying, "Data, I need data; who's got data? I don't want anyone coming into my office unless they come with data" (Figure 14).
4. An ability to define big and difficult

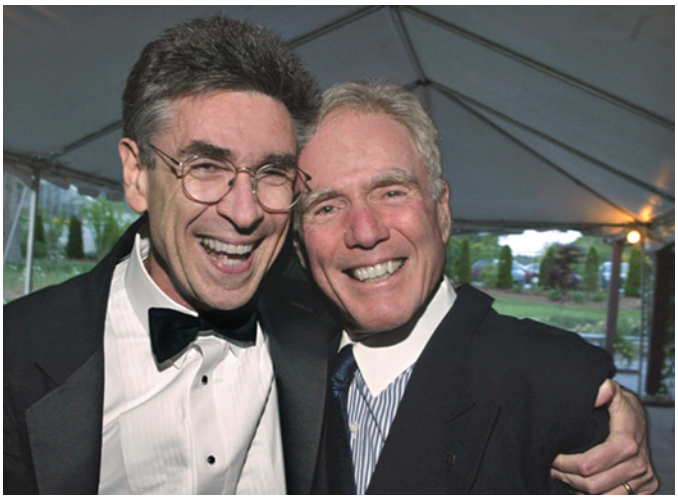

Figure 15
Bob with Ralph Snyderman.

questions and to work unceasingly to answer them. Bob describes "hovering" over a research question until the challenge to answer it becomes part of his life.

5. A willingness to develop new technology to answer such questions rather than using established technologies to find questions to answer. As Joe Goldstein put it, "There are very few scientists in the world who have commandeered a field the way Bob has. He has never wavered from the belief that the β-adrenergic receptor is the most fantastic molecule in the body. There is nothing complicated about the secret to Bob's phenomenal success — focus, focus, focus; and keep digging deeper, deeper, and deeper."

6. Bob has a joyful exuberance and openness and total engagement.

7. A deep commitment, loyalty, and caring for his trainees, all of whom felt they were the most important to him and doing the most important project.

8. A remarkable comfort with learning from others, even from his newest trainees; an appreciation that their ideas are as important as and often more important than his.

Overall, Bob has a true delight in his profession, an insatiable quest for deeper understanding, and a love for and commitment to those around him. We'll never know the mystery of what makes Bob Bob, but all these characteristics add up to Robert J. Lefkowitz being a most remarkable human being, a foundational scientist, a mentor extraordinaire, a father, a grandfather, a husband, and my dearest friend (Figure 15).

It gives me great pleasure to introduce this year's recipient of the Kober Medal, Robert J. Lefkowitz (Figure 16).

Figure 16
Bob in his lab.

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