Focus on the Research Journey

AN INTERVIEW WITH ROBERT J. LEFKOWITZ, MD, SCIENTIST, MENTOR,
AND RECIPIENT OF THE 2007 NATIONAL MEDAL OF SCIENCE

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Being presented with the 2007 National Medal of Science and receiving “recognition from the President of the United States on behalf of the citizenry” was, says Robert J. Lefkowitz, MD, “the most exciting moment in my professional career.” In a September 29, 2008, ceremony at the White House during which 7 other researchers were also recognized, the Howard Hughes Medical Institute investigator and James B. Duke professor of medicine and biochemistry at Duke University in Durham, North Carolina, was honored for, the citation reads, “his discovery of the seven[-]transmembrane receptors, deemed the largest, most versatile, and most therapeutically accessible receptor signaling system, and for describing the general mechanism of their regulation, influencing all fields of medical practice.”

Dr. Lefkowitz has researched plasma membrane receptors since the late 1960s when, he notes, “There was a great deal of skepticism as to whether [receptors] even existed.” Working then at the National Institutes of Health (NIH) under the guidance of Drs. Jesse Roth and Ira Pastan, Dr. Lefkowitz says he got his “first taste of success” by proving the existence of adrenocorticotrophic hormone (ACTH) receptors in “one of the very, very first examples of a membrane-bound receptor binding site being demonstrated directly by a ligand-binding approach.”

When he returned to research years later, convinced that “the future lay in studying these receptor molecules,” he examined adrenergic receptors because of their relevance to his clinical practice in cardiovascular medicine. This work eventually led to the isolation of both adrenergic and other receptor genes. Building upon these discoveries and involving students and fellows from across medical disciplines, Dr. Lefkowitz’s lab has identified 2 protein families affecting receptor performance: G-protein coupled receptor kinases (GRKs) and β -arrestins. The lab’s current research focuses on the “bi-functional” nature of β -arrestins, their ability to turn off protein signaling to receptors while also being “able to signal in their own right.” With relevance for research into AIDS, taste, and drug tolerance, to name just a few areas, the proven and possible applications for Dr. Lefkowitz’s work are as wide ranging as the National Medal of Science citation implies.

That award is the latest in a long list of honors Dr. Lefkowitz has earned throughout his career; he was also recently awarded the 2007 Shaw Prize in Life Science and Medicine and the Albany

Dr. Lefkowitz receives the National Medal of Science from President George W. Bush.

Medical Center’s 2007 Prize in Medicine and Biomedical Research. “I always receive these awards thinking that this is recognition, not just of myself, but of the large group of students and fellows that I have trained in my long career,” Dr. Lefkowitz says. Beyond personal or group recognition, he observes, “The giving of awards ... raises the profile, the visibility of scientific endeavor ... the citizenry need to know the importance of funding basic and translational research.” Dr. Lefkowitz’s academic successes have also inspired a sense of local pride in a North Carolina community often focused exclusively on sports accomplishments. He believes that high-profile awards offer an opportunity for young and prospective scientists to see role models pursuing “attractive and satisfying careers in research science.”

Clinic to Lab with a Translational Perspective

Dr. Lefkowitz found his role model early. Inspired by his family physician, he dreamed from second or third grade onward of being a medical practitioner. He enjoyed the clinical aspects of his medical training at Columbia University, New York, New York, so much that he passed up all opportunities to take research electives and focused solely on clinical studies. His career took a different turn during the Vietnam War’s doctor draft; landing a coveted position at the NIH, he sought to bolster his future applications for academic physician positions with research experience. “The first year was a complete disaster,” he reports, “and so I pretty much decided that [research] wasn’t for me.” But by the time he left the NIH to complete his residency training at Massachusetts General Hospital in Boston, he says he found himself “bereft of that intellectual stimulation which had come to me from analyzing experimental data,” and he “realized that research needed to be a part of my career.”

Arriving at Duke in 1973, Dr. Lefkowitz juggled time in the clinic and the lab but gradually increased the time he spent in the latter. Finally, “at age 60, I hung up my stethoscope and became 100% research.” It was a difficult decision motivated by the realization that he was becoming “out of touch with cutting-edge clinical developments.” He still misses the clinic: “I always feel like a physician, I think like a physician, but the reality is that I’m all in the lab these days.”

Having bridged the worlds of basic science and clinical work for so long, Dr. Lefkowitz nevertheless hesitates when asked if he

¹ Wiley-Blackwell, Malden, Massachusetts, USA
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himself is a translational researcher. He says, “I think the classical translational researcher would be somebody who is perhaps working on a cellular molecular level but wants to understand the process of heart failure and come up with drugs to treat it. Well, that certainly doesn’t describe me.” Although he considers himself a basic researcher, to the degree the term describes one “who seeks to understand some [physiological] process in molecular or cellular terms without any regard” for the clinical implications, that label does not describe him either. Dr. Lefkowitz sees scientists like himself as falling into a different category of translational researcher. He explains, “You’re doing basic research, you’re not necessarily looking for a way to treat or understand the disease, but, because you’re trained as a physician—and a physiologist—you have to think in those terms. You can’t help but try to put your basic science findings into that sort of translational and clinical framework.”

While in the past much of “the translation was being done by others using [his] science,” Dr. Lefkowitz says he is now trying to do some translation himself. In 2008, together with his colleague Howard A. Rockman, MD, and 3 senior postdoctoral fellows, Dr. Lefkowitz formed a biotechnology company, Trevena, that allows him to apply his discoveries. He says, “It’s become clear that it’s possible to develop ligands—drugs—which can preferentially signal down β -arrestin pathways or G-protein pathways. Those could provide very important new classes of therapeutic agents.”

The Research Journey

This new venture represents the latest step in what Dr. Lefkowitz terms his “research journey.” Working back from recent experiments to the lab’s first project 40 years ago, he sees a continuous journey without “big leaps” or “changes of field”: “One of the things that you find in science is every time you answer a question you posed for yourself, if it’s a good question, you immediately unearth a number of new questions which you couldn’t have thought even to frame—or ask—until you answered the first one.” As the questions and projects have grown exponentially, Dr. Lefkowitz has followed his interests. While acknowledging that it is possible that roads not taken might have yielded even greater discoveries, he says he derives “a great deal of pride in the fact that we’ve been able to open a number of new fields at different phases of the research and that each [experiment] has flowered from the previous one.”

In the evolving world of receptor biology, one’s research vision needs to adapt to new findings. Dr. Lefkowitz believes in a basic appreciation that, with every experiment, one is illuminating only a small piece of a much larger picture. “When we say that we’re going in a whole new direction,” he explains, “it’s not that we were wrong earlier; it’s just that the information was incomplete.”

Also critical to his research is what Dr. Lefkowitz calls an “attitude of discovery.” He says, “Every time I look at some experimental data with someone, I have a tremendous sense of expectancy.... The most important thing about making discoveries is to expect that you’ll make them.” He admits there are many days when that expectation is not fulfilled; nevertheless, “I come to work every morning and wonder what’s going to hit me today.”

A Rich Legacy of Mentorship

The success and prominence of his research may mean that his name and contributions are remembered for a long time to come, but for Dr. Lefkowitz the most important legacy is the training he has provided his students. “The key to [teaching],” he avers, “is interaction. Mentoring is all about role modeling.” There are many aspects to being a scientist that have to be learned by watching, he says. “You can’t read about how long [you should] keep banging your head against the wall on a problem which is not yielding [results].... There are in fact transferrable elements in the process of doing science, and the way to learn them is by being exposed to somebody who’s good at it.”

Students and fellows in Dr. Lefkowitz’s lab reap the benefits of such exposure. “I just love interacting with trainees about their experiments,” he says. In fact, as much as he enjoys research, “the primary activity is working with my students and fellows and showing them how I think and how I would approach [a problem], and all of the science and discovery in some mystical way to me is a necessary byproduct.” Of all the awards he has received, he feels that none is more meaningful than the American Heart Association Eugene Braunwald Academic Mentorship Award, presented to him, he notes, in 2006 “in recognition of the more than 200 scientists that have trained with me over the years.”

One such scientist, Walter J. Koch, PhD, now the director of the Center for Translational Medicine at Thomas Jefferson University, Philadelphia, Pennsylvania, observes, “The number one thing [Dr. Lefkowitz] gives to his students and fellows is his enthusiasm and his encouragement. ... You’d be hard-pressed to find somebody who has trained so many people who have gone on to become successful and outstanding scientists themselves.” As busy as he is, Dr. Lefkowitz makes it a point to tour his labs each day. “He won’t just walk through; he’ll talk to everyone,” says Dr. Koch, who sums up his experience in his mentor’s lab simply: “I wouldn’t be where I am today without it.”

Looking back over a career that has been and continues to be successful and fulfilling, Dr. Lefkowitz offers the following advice to young researchers: “Focus on the research journey. Cultivate a sense of expectancy and optimism. Discoveries are just lurking out there, ready to be picked up.” If Dr. Lefkowitz’s own journey is any indication, an attitude of discovery results in not just successes and recognition but also a lasting enthusiasm for research and an unquenchable desire to share that enthusiasm. **CTS**

SELECT RESOURCES

1. Laboratory of Receptor Biology, Howard Hughes Medical Institute, Duke University Medical Center: www.lefkolab.org.
2. Eight National Medals of Science awardees honored at gala, then the White House [press release]. Arlington, VA: National Science Foundation; September 26, 2008. www.nsf.gov/news/news_summ.jsp?cntn_id=112155&org=NSF&from=news. Accessed December 3, 2008.
3. President Bush Presents 2007 National Medals of Science and Technology and Innovation [transcript]. Washington, DC: White House, Office of the Press Secretary; September 29, 2008. www.whitehouse.gov/news/releases/2008/09/20080929-4.html. Accessed December 3, 2008.