

Robert Lefkowitz Godfather of G Protein-Coupled Receptors

Ruth Williams

What makes an investigator successful? This is a fascinating question that should interest virtually all of our readers. One of our motivations to publish Profiles in Cardiovascular Science is to offer insights into this enormously important issue from the perspective of people who are in a very good position to teach us about it because they themselves have attained the pinnacle of success. In the interview featured below, Bob Lefkowitz offers his perspective. His analysis of the qualities that are important for success will be a treasure trove of valuable information for our readers, particularly for early career investigators and for those contemplating a life in research. He is right that being smart (cognitive intelligence) and having ambition, drive, and focus are all very important.

However, if I had to pick just one factor that I consider crucial for success, I would pick hard work. This is, by far, the main determinant of an investigator's career. Success is 10% inspiration and 90% perspiration. One can be a genius, but if one does not work hard, the genius will be wasted. Nothing can replace hard work. Intelligence cannot. Intelligence is actually less important than hard work. The world is full of very smart people who never made it because they did not work hard. Conversely, there are many hard-working people who are successful even though their intelligence is only average, or just above the average.

I may be wrong, but I do not believe the irreplaceable role of hard work as the key determinant of career outcome is being adequately stressed upon young investigators. I believe this should be made clear to all aspiring scientists, as a life of hard work clearly is a choice that requires a specific personality, a specific set of values, and a strong commitment.

—Roberto Bolli

The human genome encodes¹ literally hundreds of G protein-coupled receptors (GPCRs), a type of transmembrane protein that binds extracellular molecules to transduce intracellular signals. Members of this enormous and diverse receptor family are involved in countless physiologic pro-

cesses and have become targets for numerous modern drugs. But when Robert Lefkowitz began his research career in the late 1960s and early 1970s, there was no definitive proof that GPCRs, or indeed any other cell surface receptors, actually existed.

Lefkowitz cloned the first GPCR gene—that of the β 2-adrenergic receptor—in 1986,¹ and the cloning of other adrenergic receptor genes followed quickly (reviewed in reference 2). This not only gave birth to the entire GPCR field (reviewed in reference 3), but it also particularly accelerated research into adrenergic receptor controlled processes, such as heart rate and blood pressure regulation.

Lefkowitz spent his career studying the regulation and signaling mechanisms of the adrenergic receptors. In 2007, he received both the National Medal of Science and the Shaw Prize (referred to as the Nobel of the East). Interestingly however, science was not his first love. In a recent interview, he told *Circulation Research* about the shaky start to his research relationship, about when it was he realized that research was his one true passion, and how he was driven to covertly indulge that passion in a hospital basement.

Finding a Passion

You Grew Up in the Bronx, New York City. Tell Me About That.

There was a movie about New York City called *The Asphalt Jungle*, and it refers to the fact there was a lot of asphalt and not a lot of trees, shrubbery, or grass. And what I remember mainly were tall apartment buildings and concrete. But, I would say I had a happy, pleasant childhood.

Were You Interested in Science at School?

It was never my intention at anytime during childhood or high school or even until the end of medical school to become a scientist. By about the third grade in public school, I had decided quite definitively that I wanted to be a physician. This was because of our family doctor. In those days, physicians made house calls, and anytime I got sick, he would come to the house, and he would have his stethoscope around his neck, and I just admired him. He became a role model.

When Did the Switch to Science Happen?

After medical school, during my time as a Commissioned Officer in the U.S. Public Health Service at the National Institutes of Health (NIH). That was actually my 2-year military commitment during the Vietnam war...on home soil. A very coveted assignment. Anyway, once I tasted research, everything changed. If it hadn't been for that experience, I suspect I wouldn't have had a research career.

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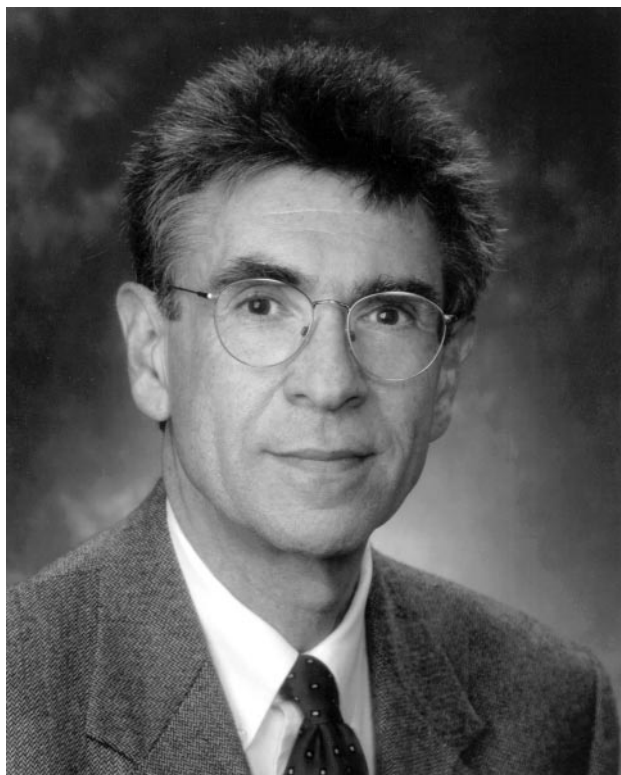


Figure 1. Robert Lefkowitz.

Was It Research From Then on?

Well, there was a little glitch. For the first year at NIH, I was miserable. All I'd known until that point was clinical stuff, which I was good at. The research, however, I was very impatient with. It seemed that I didn't have any talent for it whatsoever. I had never encountered anything that I couldn't immediately get my hands around and be successful at, but during that first year, I was getting nowhere. By the 1-year mark, I thought, "I hate this stuff. I'm going to go back to clinical training." So, I signed up to be a senior resident at the Massachusetts General Hospital (MGH). It was all set. But then, during my second year, at the NIH, the research finally began to bear some fruit, and I began to get the bug.

So You Stayed?

No. I wanted to stay, but I felt I couldn't go back on my commitment to MGH. So, with some misgivings I headed off to Boston. After 6 months of full-time clinical work, I really missed the research. I was totally miserable again.

I was facing another 6 months of clinical electives during the second half of that residency (you were not permitted to do research). But I was so miserable, that I arranged with a mentor to surreptitiously do research. This was against all the regulations, because I was being paid with hospital dollars.

I got away with it. But then one night, I was discovered by, of all people, the Residency Director. He happened to take a short cut through the basement, which is where I was working. He caught me walking along the hallway carrying a rack of test tubes. He waved a finger in my face and said, "Lefkowitz, I heard that you were doing research. See me in my office tomorrow." I could tell he was only half serious. The next day,

he and the Chairman of the medicine department slapped my wrist, but told me they wouldn't do anything.

Sticking With It

What Was the Personal High Point of Your Career?

I moved to Duke in 1973, and by the end of the first year, we'd made some discoveries that blew the receptor research wide open. But, I'd say that was the inflection point that began the steep ascent. The real peak would have been the late 1980s to 1990s. If I had to pick a single year, it would probably be 1986. Two big things happened. First, we succeeded in cloning the gene for the β 2-adrenergic receptor, the very first of the GPCRs to be cloned.¹ And second, we identified the enzyme involved in β -adrenergic receptor desensitization.⁴ In a sense, these really served as the basis for the whole GPCR field.

And What About Your Lowest Point?

I think this occurred during my first year to 18 months at the NIH. Six months after I arrived, my father died suddenly and unexpectedly of a heart attack. He was only 63, and we were very close. Meanwhile, my research, as I mentioned, was going nowhere. No matter how hard I struggled, my experiments seemed to come to no good end.

My father died in early December 1968. The last time I saw him was a couple of weeks before that when I had traveled with my family to New York City for the Thanksgiving Holiday. During that visit, I had talked with my father at length about my unhappiness and apparent complete lack of talent for research. He was an accountant and knew nothing of the particulars of my chosen career but always had a lot of common sense. He advised me to complete my time at the NIH and then go back to practice medicine, as this had always been my dream. When he died, suddenly I took it as some sort of sign that I needed to devote myself to a career in clinical cardiology. This undoubtedly had much to do with my decision to sign up for more clinical training. There is no doubt that the combination of his death and my initial failures in research resulted in one of the bleakest, most difficult periods of my life.

Despite This Terrible Low, You Returned to Research. So, What Would You Say to Young Scientists Going Through Tough Times?

Keep going! And that's not just advice for scientists. Science is just one microcosm of life. Of course, science is primarily failure. The fraction of our work that succeeds is tiny. But, in any career or life, there will be low points. I give a talk to the fellows here at Duke about once a year called, "How to deal with failure and rejection in science." The first thing I say is, "This lecture is not about your love life."

Secrets of Success

What Would You Say are Your Strengths?

Dogged persistence is one. Another is my inherent sense of enthusiasm and passion for what I'm doing. I think that's infectious. One of the things I most pride myself on is the trainees that I have mentored, which now number well over 200.

Most of the leaders in the GPCR field trained in my laboratory. To me, that fact goes beyond any of the science, and I think the reason I've been successful at mentoring is this enthusiasm and passion I bring on a daily basis to the shared endeavor. I'm very interactive. I spend my days whipping my students and fellows into the same kind of frenzy as I'm in.

So What About Weaknesses?

I think one of the things you learn in life is that strengths and weaknesses are usually the same. So, I would say that my weakness is probably my impatience—I just want to get on with it.

Indeed, I almost left science for good after that first 6 months because of my impatience. That has actually helped me to counsel people. I have seen some very bright, very motivated, young physicians, who want to try research, and they spend 6 months or a year not getting anywhere and think, “this stinks.” They are just like I was at that stage.

When Was the Last Time You Went into the Lab and Got Your Hands Dirty?

Good question. Probably in 1977 or 1978. When I set up my lab in 1973, it was just me and a technician. In those days, I had a great deal of confidence in my own bench skills, and I thought it doesn't matter who comes to work with me. I'll do fine by myself. I can produce good data. After a year, I had 4 people. Then, after a couple of years, we had 9 or 10 [people]. It became more and more difficult to do experiments myself because I would spend most of the day dealing with other people's issues. So, by the late 1970s, I stopped. I'm always threatening my team that I'll come back to the bench, but they know it's an idle threat.

The thing is that most of the techniques that are being used in my lab weren't even invented when I was at the bench! So, it's not always possible to trouble shoot.

How do You Overcome That?

In a big group, you develop a reservoir of expertise. So, at any point, there'll normally be someone who'll have the answers.

I'm surprised at how often someone will come to me and say, “I can't get such and such to work,” and I'll say, “You know, the guy at the other bench had the same problem, and he finally worked it out and told me it was such-and-such.” I

may not be doing the techniques, but I know what's going on. Success in science has nothing to do with how good you are at this or that technique.

So What is the Secret of Success?

If I knew that, boy oh boy, I'd be a wealthy man. I'd write a book about it. It's a fascinating subject, and the older you get, the more fascinating you find it. Everyone who comes to work with me is extremely smart, and most of them work extremely hard, and many do extremely well, but there is quite a spectrum of how well they do. So, what is it that lifts some people above the rest?

It has to do with a series of gifts, and not all people who are successful have the same gifts. One gift would be to be smart, but there are different types of smart. There is the smart that knows every possible fact and reads every paper in the literature. There's the smart that knows how to come up with great ideas—a raw creativity. There's the gift of synthesis—seeing lots of different findings and being able to connect the dots in a way that other people haven't done. There's the genius of being able to come up with just the right experiment. Then, there's the gift of actually being able to do that experiment. You can't get by with any one or two of these gifts, but if you have three or four, then you've got a shot.

Another gift is ambition and drive. Another is the ability to focus—that's a very important one. I tell my people, “there are four keys to success in science. The first is focus. The second is focus. The third is focus. And you gotta figure out what the fourth one is.”

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