Announcer: Welcome to the Science is the Best Medicine podcast with your host Dr. Abhinav Sharma exploring the pressing scientific and healthcare issues of our time.

Dr. Abhinav Sharma: Receptors, medications, and how to win a Nobel Prize. Today on Science is the Best Medicine podcast we sit down with Dr. Robert Lefkowitz. He's a cardiologist and scientist at Duke University. He won the Nobel Prize in Chemistry in 2012. No big deal. For describing various proteins in the human body called receptors. Now it's likely that we've all taken prescription medicines at one point or the other, but how exactly do these medications work? Well a significant majority of these drugs work by binding onto these proteins called receptors. Given how important receptors are in the body, what exactly do they do and how do they work? Let's find out.

So why don't you tell us a little bit about the journey that brought you to where you are today?

Dr. Robert Lefkowitz: Well, you might refer to me as a physician scientist and a reluctant scientist at that. I conceived the idea of becoming a physician at about eight years of age based on the role modeling of my family physician in the Bronx named Dr. Fibush, whom I greatly admired. He made house calls and I thought it was just the coolest thing. So, from about third grade on I wanted to be a physician.

I was rather precocious. Graduated college at 19, medical school at 23, was really in a hurry because I really wanted to get to the medicine. I loved medical school and I was a pretty good physician early in my career. I was asked to be the Chief Medical Resident both at Columbia Presbyterian Medical Center in Manhattan, where I did my internship, and the first year of residency after doing medical school there. And then again, I was asked to be the Chief Resident at the Massachusetts General Hospital in Boston, after doing my senior residency there.

But I graduated medical school in 1966. The Vietnam War was raging. There was a lottery draft for all men over 18, and a draft, not a lottery draft, but a draft for all physicians. You were given either one or two years of training after medical school, and then everybody went into the armed services, and just about everybody went to Vietnam for a year. It was a very unpopular war. Many of us did not want to serve, but we had to serve in some way.

One of the few ways around going to Vietnam was to gain a commission in the United States Public Health Service, which at that time as it is today, remains one of the uniform services. At that time, it was also one of the military services. It was very competitive to get these appointments, and because I had a very strong academic record, I was successful in that endeavor and gained the commission in the so-called Commission Corps of the U.S. Public Health Service, and got assigned to the National Institutes of Health for two years, along with a number of other very bright physicians who had at least a passing interest in research, which frankly was more of an interest than I had in research. I had no interest in research whatsoever. I never did research elective in medical school, I did only clinical electives because that's what I wanted to do, and I was miserable for the first year and a half of my two years at the NIH. Nothing worked. I seemed to have no aptitude for it. I was doing basic endocrine biochemistry as my first research experience. And so I made plans to complete my clinical training in medicine in cardiology at the Mass General upon completion of my two years of duty.

During the final six months of my time at the NIH, my project began to work. I published a couple of papers, got a taste of it, but was plenty happy to leave and go off to the Mass General where for the first six months I was quite happy doing intensive clinical work. But, and here was the key turning point in my career, I found I really missed the laboratory. There was something about the research experience that I just wasn't getting fulfilled by doing clinical work.

And so during the second six months of my residency, I did six months of elective time, which we had six months of electives during that residency year. I did six months in a laboratory, which ironically was not permitted. We were only permitted to do clinical electives because we were paid with hospital dollars. So I surreptitiously worked in a laboratory for six months. It was eventually discovered by the House Staff Director, who sort of hauled me before the Chairman of the department, but they only slapped my wrists. Then for the next two years I did a combination of cardiology fellowship, and research and then moved to Duke in 1973 as a junior faculty member, doing about 60 percent research and 40 percent clinical for the first few years, attending cardiology clinic, making rounds in cardiology and medicine, but then very quickly my basic research program took off, and I'd say within about five years, I was just drawn deeper and deeper into the lab. And as they say the rest is history. I wound up spending 80 to 90 percent of my time in the laboratory over the years, but continued to make general teaching rounds on the medical services here for 30 years stopping at age 60. That would be 13 years ago and I've been only in the lab since that time. So, that's how I got here.

Abhinav: So just to touch base with your inspiration for going into medicine where you saw this family doc doing house calls, do you ever think about going back into full time clinical work? Has that ever crossed your mind?

Dr. Lefkowitz: Yes, it has indeed. And on a number of occasions. I can't tell you how many over the years. I've thought about recertifying, at least in the procedures you know for cardiac arrest because it seemed … what I'll do is volunteer one or two nights a month because I used to love that kind of stuff. I'm rusty now. But I've never done it, so who knows. I'm only 73. So, you know, there's plenty of time.

Abhinav: Plenty of time to figure that out. So just to touch base a little bit on your research work, do you, you know with the time in the NIH and now with your own research laboratory, do you predominantly work with cells, with animals, with humans. What [does] most of your research work on?

Dr. Lefkowitz: It's very multi-factorial or multi-disciplined. We've hardly ever done any work with humans. Some years ago we did a little bit. I would say currently maybe 10 percent of the research is done with mouse models, of the remaining 90 percent, I would say the majority maybe of that 90 percent, maybe two-thirds to three-quarters is done at a biochemical molecular level, either with isolated proteins or isolated proteins in the form of complexes between proteins, and then the other third to a quarter is done with cells.

Abhinav: So speaking of this biochemical work, a lot of your research is focused on something called G protein receptors.

Now if we take a step back for some of our audience members who may not know, what exactly do scientists mean when they say a receptor?

Dr. Lefkowitz: So a receptor is a molecule in, or on a cell, with which a hormone, a drug, or a neurotransmitter, interacts by binding to it, with a lot of specificity, thereby initiating its actions. For hormones, drugs, neurotransmitters to work, they have to first latch on to a receptor, which is basically their gateway to the metabolic machinery of the cell.

Once they've latched on to that, much like a good analogy would be a key fitting into a lock, [you've] got to have just the right complementarity and structure. Once it fits in there into that receptor, it can then do one of two things. It can either turn a lock and make something happen, the

door open et. cetera. Let's use the example of adrenaline. So adrenaline itself binds to several receptors, which appropriately are called adrenergic receptors from adrenaline. Noradrenaline binds to the same type of receptors. These receptors at different shapes and sizes are called things like alpha adrenergic, or beta adrenergic receptors. Now things that bind to receptors can have one or two effects. They can be what we call agonists—adrenaline is an agonist. That means, when it fits into the lock, the receptor, it turns it and make something happen. In the case of adrenaline as an example it makes the heart beat more strongly and more quickly. Alternatively, they can fit into the lock, and not do anything. That would be called an antagonist, or a blocker. Many people are familiar with so-called beta blockers, which are really beta-adrenergic receptor blockers.

They fit into that adrenergic receptor lock. They don't do anything but they block the ability of an agonist like adrenaline to fit in. You might think of them as sort of a key that fits in there and then breaks off. So nothing's happening, you can't turn it, but now you can't get a regular key or an agonist in there because it's blocking the site. So that's what receptors are.

Abhinav: And so it seems that there are a variety of molecules that can latch on to the receptor and either activate or not activate the internal cellular machinery. In terms of your research on G protein Receptors, what exactly are they and why are they so important?

Dr. Lefkowitz: There are different types of receptors. Some of them are found on the cell surface, some of them are found in the cell cytosol, otherwise known as the cytoplasm, others are actually found in the nucleus.

Abhinav: Just to clarify, the cytoplasm refers to the fluid that is within each cell, and the nucleus is essentially the nerve center of all the cells, and contains all of our genetic information and material.

Dr. Lefkowitz: Nothing was known about how that worked at the time I started my research around 1970. But then it was discovered by two other guys named Martin Rodbell and Al Gilman, both of whom won the Nobel Prize, that the key link between the outside of the cell and the inside of the cell was something called the G protein. G standing for guanine nucleotide, such as GTP, which is a chemical.

Abhinav: By the way just to clarify, GTP can be used as a source of energy in the cell, and is a fundamental building block which can be used to transmit genetic information, which is stored in the DNA as it gets translated into proteins.

Dr. Lefkowitz: So GTP binds to proteins, which were properly called G proteins, and somehow that's able to relay a signal from the cell surface to the inner part of the cell. So now we had an enzyme making a second messenger, cyclic ANP, on the inside of the cell, and just upstream of that we had something called a G protein, which was sort of a relay station in the cell membrane. But we still didn't know how the whole thing got started, and that's where I came in. And what I was able to discover over a period of years, is that the first step in the process, which initiates the whole signaling cascade, was the binding of something like adrenaline, or a hormone, or neurotransmitter to a receptor, which were appropriately then named G protein coupled receptors, because these receptors link up with these G proteins, which are the relay stations.

We worked very hard to prove that such receptors existed. That took a good number of years of work, and then we used biochemical techniques to purify them, and molecular biological techniques to clone their genes, to figure out what they looked like, and where that led us to was a discovery in 1986 in which we cloned the gene for the beta adrenergic receptor, and were able to deduce its complete amino acid sequence. And what we learned from that, was that it had a very interesting and unusual configuration, wherein the protein chain of amino acids weaved across the plasma

membrane seven times like a snake.

Well at the time only one other protein was known to have an architecture like that, and that was a protein called rhodopsin, which is found in the retina, where it basically serves, if you will, as a receptor for photons of light. That's how we see. It was also known that rhodopsin coupled to a G protein, a different G protein in the retina, called transducin. So we immediately surmised that perhaps this seven-membrane-spanning-architecture of the beta receptor and rhodopsin might be a universal feature of receptors for many different neurotransmitters and hormones, like glucagon, like dopamine, like serotonin, like parathyroid hormone, and calcitonin, and on, and on and on, and over the next few years we cloned the genes for about a dozen of these receptors, and sure enough they all had very similar amino acid sequences, and they all had this seven-membrane-spanning domain architecture. And so, we deduced that there was a huge family of these seven-membrane-spanning G protein coupled receptors. Over the next decade into the 90s and beyond, people were able to obtain the sequences for many, many of these receptors and the family grew to about 1,000 different receptors including, for example, not only for neurotransmitters and hormones, and vision, but for example, for taste, sweet taste, and bitter taste and smell. There are several hundred receptors that look like this, all of which are related in structure, which mediate our sense of smell. So that's the story about G protein coupled receptors. Why are they so important? Because almost half of all drugs used in clinic target these receptors, either as agonists like adrenaline itself, or as antagonists, such as beta blockers or angiotensin receptor blocker, so-called ARBs, and on and on and on. So, that's the major importance in everyday life, other than the fact that these receptors regulate virtually every physiological process in our bodies, is that they are the targets of so many drugs.

Abhinav: So, I guess given how fundamentally important these G protein coupled receptors are, is this the work that led you to winning the Nobel Prize?

Dr. Lefkowitz: Yes, most definitely so. I think the prize was for the discoveries that I just described.

Abhinav: Going back to your time at the NIH and afterward, what were some of the challenges that you faced as a young scientist as you were going through your training, both either from a clinical aspect, or a research aspect, or even otherwise?

Dr. Lefkowitz: So, the challenges I faced, some of them were quite personal. The non-personal ones I must say were different than what are faced today. So, for openers, when I came to Duke the pay line for NIH grants was about 30 percent. That meant if you put in an application, you had about a 30 percent chance that it would get funded. Today that number is 10 percent, or even less sometimes. So, we didn't have to struggle the way the scientists did today in order to get grants. So, that was one thing that was sort of different.

For me, one of the biggest challenges was personal. So, I mentioned how much I hated research at the beginning because frankly I had never failed at anything at all, in my academic career. I was always at the top of the class, and I never really encountered anything before that I couldn't do. But I sure wasn't good at this. And then I would say about six months into that first year at the NIH, I traveled with my family, I already had a couple of kids. I traveled with my family back to New York from Bethesda, Maryland where the NIH is, to celebrate Thanksgiving with my parents. I was an only child by the way. My father had coronary artery disease and he had already sustained three myocardial infarctions over about a 12-year period starting at age 50. He was at the time 63. So, we had a very nice time together. I was very close to him and I discussed with him how miserable I was doing research. And I didn't know what to do, and he was a good guy, he was always kind of my adviser in all matters. And together we worked out a plan, where at the end he said, look you always

wanted to be a cardiologist, you had no interest in research. Why is it bothering you so much that you're not any good at it, he says, do your time, it fulfills your draft obligation, then you'll go finish your training, and you'll be the cardiologist and internist you always wanted to be. Well that made a lot of sense to me. I relaxed. I felt good about it, and back I went to the NIH with a much more positive outlook. Two and a half weeks later, he died suddenly of his fourth myocardial infarction, which was a big surprise.

So, the personal challenge for me, was that over the next few years even as I began to feel eventually that research might be the best path for me, I was kind of stuck on this last, because I never talked to my father after that, that was the last conversation I had with him. I was really stuck on this sort of pact that I had made with him, this plan for my career that we'd worked out together to become the practicing physician that I, and to be quite frank, I think he and my mother, had always dreamed of. So even as I felt the draw of research getting ever stronger over the next five years. There was a part of me that always held back, held back because my goodness, I had made this plan with my dad to be a practicing cardiologist. But eventually the pull was just too strong, and I got past that. So, that was a very, very personal kind of challenge that I faced.

Abhinav: Well thank you very much for sharing that with us. And that leads to my next question—where scientists often have families, and they have family obligations, and as you describe, the amount of work that has to go into dealing with animal research and translating is absolutely tremendous. Is there a significant difficulty in maintaining that type of work-life balance, or have you found that difficulty in balancing your research work and your life work as well?

Dr. Lefkowitz: The question is an excellent one, and I would have to say that through most of my career I did not achieve that balance. I was totally over on the side of my research in my career, and do I regret that? I can't say that I do, because when I asked myself as honestly as I can, "Do you wish you had done it otherwise?" The obvious answer is, "Well I'd have to have been a different person." For me this was clearly the way I was wired and it was extremely difficult to achieve that balance. That said, and returning to the way you phrased the question before … this was a challenge that was a lot easier in my day. In my day, people married younger, much younger than they do today, and one-career families were the rule, not two-career families. So, in such a setting, one partner was primarily committed to the family, and one partner was the breadwinner, typically in those years, the female was the one at home, and the male was out, you know foraging for food and fighting off the lions. Now that made things easier in the sense that, as long as both partners were comfortable with the arrangement, it was a partnership. So today, I counsel the young people all the time, almost everybody has a two-career family. Typically, scientists are married to scientists, physicians to other physicians, or very busy professionals. And it's a whole different ballgame and makes the work-life balance even more difficult, because everybody is juggling this stuff. I had a lot less stuff to juggle because my wife was pretty much raising the kids. And I, you know, I was there but not the way she was full time, but she didn't have to work, so she had 100 percent of her time to devote to the kids. That was the common situation then. Whereas today, it's almost invariably two-career families. That's a much bigger challenge. And so, I was never that good at the work-life balance thing, although we did successfully raise five kids, all of which I'm very close to.

In fact, I just got back this Sunday a couple of days ago from the beach where I vacationed as I do every summer with all five of my kids, their spouses and my six grandkids all in one house, and that's great family time. Now that I'm a bit older and maybe not quite so professionally engaged as I once was, I think I have a much better balance.

Abhinav: So, what advice do you give to young scientists who come to you today and say we're in a two-career household, having challenges with the work-life balance. Looking back and reflecting on your career, are there pearls of wisdom that you can impart?

Dr. Lefkowitz: Not much I'm afraid, because again I didn't have to face what they are facing. I could always pretty much slough it off on my wife because she didn't view it as sloughing off. That was just my job was to, you know conquer the world. Her job was to raise these great kids. So I'm not much of a source of counsel to them other than to the obvious platitudes, which is that you need to respect each other and try to share as equally as possible. And I must say, up until recent years, I didn't know that I ever saw a couple raising children where I could honestly say that from what I could observe, the male and the female were co-equal partners. I saw some that got close maybe 55-45, but I never saw one where the guy fully pulled his weight. But I have to say that in recent years, I have seen some and even a couple where the guy was pulling more of the weight, but that's a relatively recent development.

Abhinav: Fair enough, so things definitely seem to have shifted over time since your training to what you see right now.

Dr. Lefkowitz: They have. In my medical school class '62, there were 110, there were eight women. I happened to know that in the class 10 years before, that would be '52, there were four women, and I know that Duke Medical School today is significantly above 50 percent women in the class, 55, 56 percent something like that. And that's typical of many medical schools. So yes, it's a whole different world.

Abhinav: Well that's absolutely phenomenal, and now as we sort of wrap up this podcast here, there's a new section we're going to try … rapid-fire you can answer with one or two words, or a sentence if you will. So let's go.

As the Nobel Prize laureate, do you have a secret handshake that you'd use with other Nobel Prize Laureates?

Dr. Lefkowitz: No secret handshake, but I think there is very much a feeling of affinity for the other laureates because of a shared experience that's so unique, that you have.

Abhinav: Fair enough, so do you actually have the real number to customer service or you know, to parking. You get little perks that way?

Dr. Lefkowitz: Yes. In fact, I have my own parking spot, paid for by the Dean, over in the Sans building lot. So, I got my own parking space that they even pay for, it has a sign on it with my name and my decal number. I told her I was very appreciative. But I frankly didn't really need my own parking spot. I said what about my own toilet in my office? But I didn't succeed in that.

Abhinav: Well life's a bunch of compromises I suppose.

Dr. Lefkowitz: Indeed, it is that.

Abhinav: So the final question. are you on Twitter? Social media is that a part of your life?

Dr. Lefkowitz: No I am not on any social media; I pride myself on this. However, I shouldn't say that, about four or five years ago, one of my daughters, one of my five children set up a Facebook page for me, which I last visited about a year and a half ago, I don't remember why. So, I don't go on Facebook very often even though, as you can imagine, all my kids and grandkids and whole family is on there. In fact, the day I won the Nobel Prize, you get called at five o'clock in the morning East Coast time, you're told you can't tell anybody about it until the official announcement one hour later, 6:00 a.m. East Coast Time, 11:00 a.m. Stockholm time. As soon as I was able to, as

soon as that announcement was made, I tried calling my kids who live around the country, but I was only able to tell two of the five because the other three knew about it already from Facebook. So I kind of regret it.

Abhinav: You got scooped by Facebook.

Dr. Lefkowitz: You got it.

Abhinav: Well Dr. Lefkowitz it's been an absolute pleasure having you here. I really appreciate your time, and thank you very much for coming on the podcast.

In this episode we talked with Dr. Robert Lefkowitz about the fundamental importance of receptors in the human body. It always amazes me at how something so seemingly small can play such a big role in our health, specifically that most drugs that we consume today in some way, shape, or form, bind to these receptors in order for them to exert their activity on the human body. We also heard that even a Nobel Prize Laureate can have difficulties in getting a private washroom.

Thank you very much for everyone who made today's episode possible. This is your host Abhinav Sharma, and I hope you enjoyed your dose of Science is the Best Medicine podcast.

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