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By Megan Scudellari

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## Q&A: The molecular locksmith

### National Medal of Science laureate Robert Lefkowitz was one of the first to show that receptors were real protein structures

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Robert Lefkowitz, Duke University biochemist and Howard Hughes Medical Institute (HHMI) investigator, believes that serendipity is one of science's greatest allies. It has certainly smiled on this professor of medicine, who will receive the National Medal of Science in three weeks for his work in isolating, defining, and characterizing G-protein-coupled receptors and their related signaling pathways.

[Lefkowitz](#) has spent more than 35 years studying adrenergic receptors, a class of GPCRs targeted by compounds like epinephrine and norepinephrine, and has published more than 800 papers on receptors and cell signaling. Today, GPCRs are the most common target of therapeutic drugs, including psychoactive drugs, antihistamines, opioids, and others. On the eve his national award, Lefkowitz took some time to discuss the past, present, and future of cell receptor biology with *The Scientist*.

**Robert Lefkowitz:** One of the interests I had early on was to show that there actually was such a thing as a receptor. At the time I started my work, it was not generally accepted that these things really existed. Raymond Ahlquist, a distinguished classical pharmacologist of the mid-20th century, came up with the idea that there was more than one type of adrenergic receptor, which he called alpha and beta. In 1973, after he and I had attended a symposium together -- I was just a young buck -- I was talking about the idea that receptors were real things, that they must be proteins, and I was trying to study them. In response to [my ideas], he wrote, "This would be true if I was so presumptuous as to believe that alpha and beta receptors really did exist. There are those that think so and even propose to describe their intimate structure. To me they are an abstract concept, conceived to explain observed responses of tissues produced by chemicals of various structure." Ahlquist, the father of this whole field, in fact did not believe these were real things! My first interest was to prove him wrong.

**The Scientist:** One of your most highly-cited papers is a 1980 paper in the [Journal of Biological Chemistry](#). [Ed. note: The paper has been cited more than 1,150 times.] Why was this such a foundational paper?

**RL:** That was an interesting era. We had developed these radio ligand binding methods for studying the receptors. For the first time, one could study receptors directly. As we were examining competition binding curves, we observed some anomalous properties: It looked like there were two affinity states for binding agonists. Intuitively, I developed an idea, together with a graduate student, Rusty Williams, that we were essentially seeing a reflection of two different forms of the receptor: One was a low-affinity form that might be a free receptor, but the high-affinity form might be a complex of the receptor and the G-protein. But I certainly did not have the mathematical or computer chops to formalize that intuition, and through a very serendipitous set of circumstances, I managed to attract to my laboratory a brilliant young man named Andre De Lean, the first author of the paper. He put it all together using computer modeling, and we came up with this ternary complex model, which in fact confirmed that intuition: The agonists, but not antagonists, when they bound to the receptor would promote coupling of the receptor to a G-protein. That would then form a high-affinity productive complex. We put forward this conceptualization called the ternary complex model, and it has really formed the basis for the analysis of that kind of data to this very day, and continues to be cited at a reasonable rate, even though the paper is almost 30 years old. I take a great deal of pride in that.

**TS:** In our August issue, *The Scientist* featured a story on [orphan GPCRs](#). The hunt began in your lab. How did it start?

**RL:** It's one of my favorite stories. It was a classic example of serendipity, which if you spend time in science, you learn that serendipity is your ally. We had just cloned the  $\beta_2$  adrenergic receptor.

**TS:** That was the first GPCR, a [7-transmembrane receptor](#), to be cloned?

**RL:** Correct. Technically the first one was rhodopsin. It's so abundant in the retina that in the early '80s several groups determined its sequence without cloning -- they had grams of this stuff. All other 7-transmembrane receptors are basically trace contaminants of the cell membrane, and that's why nobody had ever gotten any structural information about any of them until we had done the  $\beta_2$  adrenergic receptor. When we found the  $\beta_2$  receptor, it looked like rhodopsin. People, including us, were shocked. It immediately suggested that all these G-protein coupled receptors would look like this.

So we cloned the  $\beta_2$  and had the cDNA for it. We did genomic Southern blots: We took genomic DNA and the entire cDNA for  $\beta_2$  and did a [Southern blot](#) looking to see if the cDNA would hybridize to anything else in the genome. We reasoned that if our hypothesis was right, that all these G-protein coupled receptors are going to look like the  $\beta_2$ , we should pick up some other [receptor sequences]. In a high stringency blot, which will disrupt all but the most high affinity binding, there was only one line of any real substance. We made the obvious conclusion that this was the so-called  $\beta_1$  adrenergic receptor: Functionally, there is nothing closer to the  $\beta_2$  than the  $\beta_1$ , so this had to be the  $\beta_1$ .

So we got it sequenced and expressed it in cells, but it does not bind beta adrenergic drugs. Now we're stuck. It's clearly a member of this family, but it isn't the  $\beta_1$  adrenergic receptor. We have no idea what it is. We publish it anyway, saying we don't know what it is. It's the first orphan.

**TS:** A regularly-touted statistic is that half of all modern drugs target GPCRs. What characteristics make that the case?

**RL:** Some aspects of that we understand, some we don't. What we understand is that these G-protein coupled receptors, they regulate virtually every process in the body, so of course they're good targets.

What's not so obvious is why they are so druggable. It turns out that it isn't all that hard to come up with compounds that fit into this seven-membrane structure. For as yet unknown biophysical reasons, it seems to be quite feasible to find compounds which fit in them, to both stimulate them or block their stimulation.

**TS:** What are some exciting directions in the field right now?

**RL:** One of the things people are all excited about is applying structural biology to the field. The field has been kind of impervious to structural biology: These are membrane proteins and they are very hard to work with. The best crystallography labs in the world have and continue to take a shot at this, and nobody can break it. But finally a year ago, the first structures of a GPCR, aside from rhodopsin, appeared by a guy named [Brian Kobilka](#) [of Stanford University]. He has worked on the problem for 15-18 years, and he finally got it and everybody's all excited. The first structures, frankly, don't teach us a lot, even though they're beautiful structures, because they look about the way we thought. But where the field is going is to try to understand the structural basis of signaling. The structure that he did is of the quiet receptor, and what people want is the activated receptor. I predict within a year he'll have it.

Another direction the field is going is based on the recent discovery of [allosteric effectors](#). By binding at a distance, and not by direct competitive binding, you can change the properties of receptors, and that has a whole lot of potential in the future for designing drugs.

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