G-protein–coupled receptors (GPCRs) are transmembrane proteins that bind ligands on the outside of the cell and, in response, activate their associated G proteins on the inside of the cell, initiating signaling cascades. There are literally hundreds of different GPCRs activating hundreds of different signaling cascades that regulate as many physiological processes in the body as you can think of.

But, studying these important proteins is challenging. For one thing, they are firmly imbedded in the plasma membrane making them tricky to purify. For another, they change conformation when binding ligands making it difficult to determine their structure. Brian Kobilka has conquered both of these challenges, perfecting the art of purifying a GPCR called β2-adrenergic receptor—which regulates blood pressure, heart rate, and other processes—and determining its crystal structure. In 2007, he published the structure of the receptor in an inactive state bound to an antagonist ligand and in 2011, he determined the structure of the agonist-bound receptor interacting with a G protein—articles that together tell a complete story of GPCR activation from outside to inside of the cell.

In the early 1980s, Kobilka was starting out his scientific career in the laboratory of Robert Lefkowitz, who has also been the subject of a Circulation Research Profiles in Cardiovascular Science article. Together they cloned the gene for the β2-adrenergic receptor, which opened the gateway to a new field of GPCR biology. Kobilka and Lefkowitz have been dedicated GPCR researchers ever since, and in 2012, were together awarded the Nobel Prize in Chemistry for their contributions.

Kobilka, who is a professor of Molecular and Cellular Physiology at Stanford University in California, spoke to Circulation Research about what winning the Nobel meant to him, his love for his job, and the importance of remaining optimistic and open minded in the face of difficult scientific challenges.

Where Did You Grow Up?
I grew up in a small town called Little Falls located next to the Mississippi River right in the middle of Minnesota. Although
it was a town of 7000, I thought it was more like a city from the perspective of it being the biggest town in the county.

Tell Me About Kobila Family Life
It was a very quiet childhood. We did not have access to a lot of the things you get in a big city, but it was very pleasant and as kids we roamed around on our bikes without parental supervision most of the time.

My father owned a bakery. It was something his father had started. And my mother was a cake decorator at the bakery. She was very good, very artistic. The bakery had quite a good business. It was not only a store, they also sold goods to supermarkets, schools, and restaurants.

Were You Expected to Take Over the Family Business?
No, there was absolutely no pressure for me to take over the bakery. It was a very hard job. My father worked 7 days a week and often had to go in the middle of the night if someone had not shown up for their shift. I do not think he ever wanted me to take over the bakery.

When Did You Become Interested in Science?
In the beginning, I was more interested in being a doctor. I admired my pediatrician. He was someone who took care of everybody when they were sick and was respected in the community. I looked up to him and thought that was a great job.

Then in high school I realized that the sciences were important for getting into medical training, so I took as many science courses as I could, and it turned out I enjoyed all of them. But I did not know anyone that did research, so I thought science was, more or less, a means to an end as opposed to being a career in itself.

At What Point Did You Change Track Toward Science?
It was during my very first quarter at college. I had an introductory biology class and the professor who taught it, his name was Conrad Firling, just loved what he was doing. He was a great lecturer and he encouraged us to consider doing research, while we were undergraduates.

I had never thought of doing that, so I went to speak with him, and he said he would give me a try. I started working in his laboratory probably in the second quarter. The first job was to be the dishwasher. Then, if you did well at that and you followed instructions, you could begin to do some other more interesting things.

Through my experience with him, and some research projects I did with professors in Chemistry, I began to think of basic research as an alternative career.

I actually applied to both medical schools and programs in Biochemistry. Partly as a fallback in case I did not get into medical school, but also partly because I thought it would be a great career.

But You Went to Medical School…
Yes, and I went on a public health service scholarship. It paid for medical school but it also obligated me to be a clinician for quite some time. I was obligated to serve in the public health service, so although I became more and more interested in research while in medical school, it was out-of-bounds for me. However, when I was finishing my residency, the Reagan administration pretty much abolished the public health service, so there was no place for me to serve out my promise. Instead, they allowed us to do a different kind of payback that meant I could simply go and practice academic medicine for 4 years. That was a stroke of luck. I went from being obligated to train as a practicing physician to being obligated to train as an academic physician.

I pursued an area that I thought was the most interesting clinically, which was intensive care unit cardiology. I also realized that there were several cardiology programs that allowed you to do basic research as part of your training. One of them was at Duke University, and I chose it because they were the most proresearch of all.

Why Did You Choose Robert Lefkowitz’s Laboratory?
As an intensive care unit physician you use a lot of drugs that work on sympathetic and parasympathetic receptors, and the Lefkowitz laboratory was doing cutting edge research on those 2 types of receptor.

I interviewed with a number of people, but I actually did not interview with Bob. The 3 times I visited, he was not there. However, I spoke with Bob on the phone and it was pretty clear that they were doing the things I really wanted to do. The decision was pretty simple.

You Have Worked on G-Protein–Coupled Receptors Your Entire Career. Have You Ever Considered Another Topic? Or Even Career?
Once I had been at Duke doing research for 3 years, I knew that it was what I wanted to do. I do not think there was ever a time when I was really debating a different career.

As for trying another topic, no, because I never thought that the problem was solved or that we had all the answers. In fact it seems the field is out-pacing any investigator. It is more complicated and there are more things for us to know about. It is kind of exhausting just trying to stay in the field because it does not seem like we are ever going to answer all the meaningful questions about structures and mechanisms.

Why Did You Move to Stanford?
The school had a good reputation, particularly for attracting great graduate students and postdocs. I thought this would give me the best chance to succeed because I would be able to choose the best young people to work in my laboratory.

I also love the west coast. It is a great place to live. And they offered me a job. Another attraction was that I was going to be part of a brand new department. I would not be the newest person in the department. We were all new, and that was exciting.

What Has Been the Highlight of Your Career: The Nobel Prize, Cloning the Receptor, or Something Else?
What the Nobel prize does for you is that it tells you other people think you have done something of importance. All
scientists would like to think that, but we also do not really know it because we focus on such a small area of science. At some point I began to realize I had a good reputation in the field and people liked what I did, but I did not really know if my work was respected. It is really nice to realize that people appreciate what I have been doing for the past 20 years.

That is a very different kind of excitement to, say, cloning. There was, I would say, 3 or 4 times in my career when we climbed over big hurdles. Cloning was one of them, and it was an amazing effort by a team that worked really well together in the Lefowitz laboratory. That was really satisfying. And then there was another goal, which was to get our first crystal structure of the inactive state. That was another one of the really satisfying accomplishments.

But of all of the scientific accomplishments, I would say the one that I felt really best about was the receptor G protein complex structure because that really told us more about transmembrane signaling by G-protein–coupled receptors than any of our previous discoveries. It captured a receptor in the act of transmitting a signal from outside the cell to the inside, and that really felt close to having completed a story.

Of course it is only a fraction of G-protein–coupled receptor biology in general, but we had solved a discrete question, which was satisfying. It was also satisfying because it was so difficult to get everything to work and was such an amazing team effort. People contributed in many different ways and it turned out that most of those contributions were essential. So from many perspectives, it was a very satisfying achievement for the team.

Given the Difficulties, How Did You Maintain the Will to Keep Going?
We felt we knew more about these proteins than anybody. We had built up so many tools over the years that would help us, and we had made a lot of incremental achievements, so we thought we were making progress. Maybe occasionally we would have set backs but, in general, there was a forward momentum. Also, both my collaborator Roger Sunahara and I are very optimistic. We take disappointment fairly well and when things go wrong we think to ourselves, well we have not tried everything yet. We will get there. I do not think we ever really thought of quitting.

What Has Been the Lowest Point in Your Career?
I would say that one of the times that was the most disappointing was losing funding from the Howard Hughes Institute. To me it meant that there were people who were really gifted productive scientists who had made a decision that I was not someone they wanted to continue to support. That was a big blow to my ego, as well as my pocket book. I struggled a lot and had to let some laboratory staff go.

How Did You Bounce Back?
I wrote a lot of grants. I had some support from my department, although it really did not have a lot of financial support to give. I also had some support from people in industry—there were a couple of Danish pharmaceutical companies, Lundbeck and 7TM Pharma, that gave me gifts without asking for anything in return, which is quite unusual. I also always had an RO1 from the National Institutes of Health, but it was never enough on its own.

What Are Your Biggest Strengths and Weaknesses?
Erm... I am not sure I want to answer this question! Ok. I would say my major weakness is probably writing, and it is so important—you are always having to write grants and articles. But it takes me so long. Even composing an e-mail can be a task for me. I think of the different ways it could be interpreted and then, after spending all that time thinking about it, I might still have errors with my grammar and spelling. It holds me back, and I am always behind on writing projects.

Do You Delegate Writing Tasks?
Most often I do not. Part of writing is the way you craft a story, and sometimes you only get to know the right way to present a project by actually struggling with different ways to organize and illustrate the material, so it is hard for me to delegate in that respect. Maybe that is also a weakness?

And Your Strengths?
One of the contributions to my success, I think, is that I really love bench work, and I have always been relatively good at it, for whatever reason. I love doing experiments and while I do not do as much as I would like to anymore, there are still things I do in the laboratory and it has given the project continuity. For example, by 1995, we had developed methods to express and purify the receptor. If only one person had these skills and left the laboratory without transferring that knowledge to somebody else, well then the project could not have been sustained. I think the fact that I have been one of the people who were actually doing the work has allowed the project to continue through many different graduate students and postdocs that have come and gone. Doing laboratory work for such a long time has also given me the skills to troubleshoot and probably helps me to solve problems that young people starting out in my laboratory might be having.

Another strength, and I do not really know if it is a strength or just good fortune, is that I have had great people in my laboratory over the years and, I guess, I had some role in selecting them. I have also had a fantastic group of collaborators who have made essential contributions. My collaborators have invested time and resources, and contributed ideas to projects that are very high risk without any guarantee of success. So I guess one of my strengths might be that talented people like to work with me, although I am not sure why this is.

Who Has Inspired You?
I would first of all say my father. He was just a really good person. I think some of the ways I work with people and mentor students and postdocs I have learned from him. He would always try to keep his people happy and motivated and try to get them to do their best. The only time he really got upset with people was when he felt that they were not working to their full potential.
As for scientists, Conrad Firing and Bob Lefkowitz had important impacts on my career. What they both taught me was that you have to find your own way of doing things. Neither of them demanded that I do things their way. They both encouraged their students and postdocs to be creative and independent and that was a really important lesson to me.

**Do You Have Advice for Young Scientists?**

If you want to be successful, you have to do something you really love. I think one of the reasons I stuck with the β2-adrenergic receptor is that I was very interested in the problem. I believe that if you are working on something just because you think you can do it and it is relatively straightforward, you may not develop that passion for your work and it may not be as rewarding—it probably will not be. I am not saying you should choose a problem that is intractable, but I think you should choose a problem that you think is important and interesting and keeps you challenged.

**How Important Is Hard Work?**

You cannot succeed without working hard, but I do not think work should completely consume you. For example, when I started out I had a young family and when we moved to Stanford, my wife, who has been one of my closest colleagues for decades, decided to go back to medical school. So for the years that she was at medical school and doing her residency, I did a lot of the parenting—I took the kids to soccer, I cooked most of the meals. I had other aspects to my life besides science.

I also think it is important to stay healthy. People who know how I eat would not necessarily agree that I am healthy, but I do exercise and I think that it is important to have more than one dimension to your life.

**What Sort of Exercise Do You Do?**

I really like bicycling. I have been doing it since I was a kid. I did my first long bike tour when I was 14. I went to Yellowstone National Park and back with a friend. I have also been across the country and toured around England and I have done a little racing. I mean, I am not a gifted athlete by any means, but I enjoy cycling a lot. I run and swim also. I am fairly active in general. I like to do some sort of activity several times a week and if I am not doing something related to work then I am generally exercising.

And I find that often when I am running or riding my bike, I can think through problems that we are having in the laboratory.

**Any Other Advice?**

Scientific problems nowadays often cannot be solved with just one form of expertise, and it is important for people to understand that they have to work collaboratively. I think this is going to be even more important in the future as funding will not keep pace with scientific challenges and may even be contracting. So, you have to find the right colleagues and develop good relationships with people across disciplines. That way even if you do not know how to do something, you can still be part of the solution. You might even learn something new in the process.

**Disclosures**

None.

**References**

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