through Advancing Innovative Neurotechnologies] Initiative, announced by President Obama in 2013, and the Human Brain Project in Europe, also announced in 2013, might be more timely.

How does Sweden, home to the Nobel prize, treat its laureates?
The prize is most revered in Asian countries. If you have a Nobel prize and you visit China or Japan you are received as if you were a king. In Sweden less so, because the mentality is that we should all be treated as equals. A friend of mine once requested a table by the window when making a reservation at a restaurant to celebrate my birthday and mentioned that I was a laureate, only to be told that it made no difference. And you don't get better seats in the theatre, either. Here in Lindau it is different, of course. But I would like to see more people giving talks here, even if they are not recipients of the prize, because it shouldn't be an institution for ageing scientists. You want students to be exposed to the best there is.

What tips would you give to a young scientist today?
Science should be fun: you should enjoy what you do. In this era of 'big science', there are still areas in neuroscience where an individual or small laboratory can make an important contribution, such as the study of the sensory and motor systems and the cortical circuitry underpinning the higher function of recognition of objects and places. My advice for an undecided brilliant young person looking for an area of research is to enter the field with the sincere intention of helping to solve the intriguing questions of how the brain works.

What is the most important lesson you have learnt?
To respect other people's point of view, even if you disagree. Lots of discoveries in science have been met with claims that they must be wrong, but it is a mistake to say that on the grounds that something doesn't agree with dogma. I have a deep sense of respect for everybody. From a janitor to a president, I deal with each person in the same way. ■

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JONATHAN SPRAGUE/REDUX/EYEVINE

Q&A Brian Kobilka

Stuck on structure

Brian Kobilka shared the 2012 Nobel Prize in Chemistry with Robert Lefkowitz for their studies of G protein-coupled receptors. He is professor of molecular and cellular physiology at the Stanford University School of Medicine in California. Haya Jamal Azouz asks Kobilka what it takes to spend 30 years answering a single research question.

What are G protein-coupled receptors (GPCRs) and why are they interesting?
GPCRs are proteins found on the surface of all cells in the body that recognize and bind hormones and neurotransmitters. Their principal purpose is to transmit a signal to active proteins on the inside of the cell, thereby changing the cell's behaviour. There are more than 800 GPCRs in the human genome. They mediate the majority of the body's response to hormones and neurotransmitters, and are responsible for the senses of sight, smell and taste. GPCRs are involved in so many aspects of normal physiology, including homeostasis. It is interesting to understand how protein structures mediate signalling behaviours; understanding the structures may be helpful in developing more selective and effective drugs for these receptors, which represent approximately 30% of current drug targets. My initial interest in β-adrenergic receptors came from my clinical experience using β-agonists to treat asthma and β-blockers to treat heart disease.

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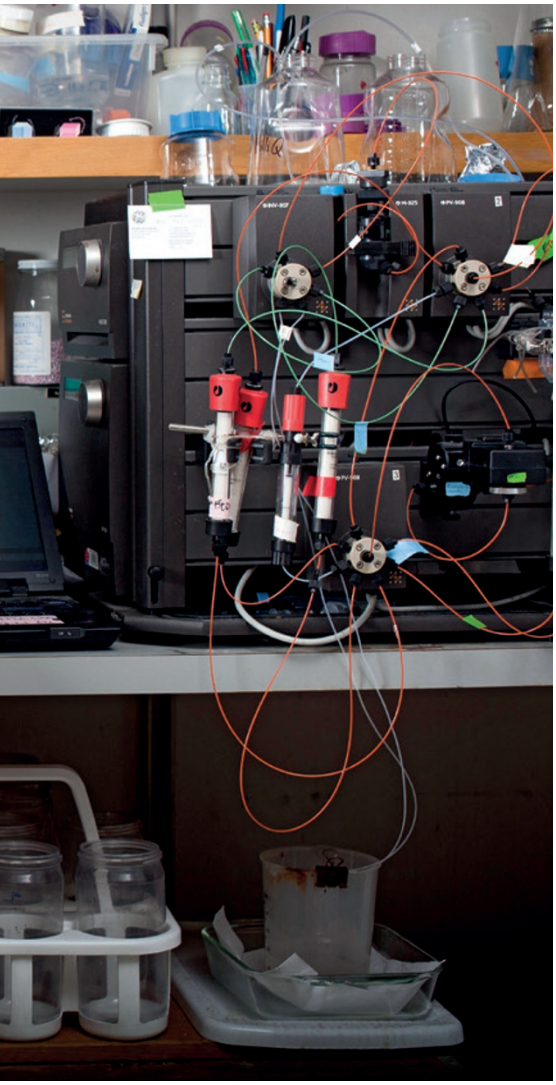

Why is the structure of GPCRs so hard to crack?
To determine the structure of proteins such as GPCRs it is necessary to crystalize the protein. The diffraction patterns of X-rays that pass through the crystals can then be used to determine the crystals' 3D structure. The first GPCR structure to be solved — rhodopsin, which is a protein in the rods of the retina that can respond to a single photon of light — was an incredible challenge. Even though rhodopsin is abundant and is one of the most biochemically stable GPCRs, it has relatively little polar surface area, which makes it difficult to form crystals. Solving the structure of the β-receptor, a different GPCR that is activated by the hormone adrenaline, was even more challenging. Unlike rhodopsin, there is no tissue in which the β-receptor is expressed at high levels so we had to use cultured cells to produce the receptor. The β-receptor is flexible and biochemically unstable and it is difficult to obtain enough protein to allow crystallography trials.

Did you expect the project to be so tough?
No! When we set out in the early 1990s, we didn't know the first thing about crystallography or about the biochemical behaviour of these proteins, for example whether they were dynamic or unstable. Using a technique called fluorescence spectroscopy we were able to get structural information that provided insight into why it was so difficult to crystallize the β-receptors. We learned that the β-receptor did not operate as a simple two-state on–off system, but that its shape was complex and flexible. For proteins to crystallize they must all be in the same conformation — that is, they must all have the same shape — but our fluorescence studies suggested that the β-receptor did not exist in a single conformation even when bound to an antagonist or agonist. A population of receptors in solution have different shapes — subtle differences, but sufficiently large to prevent crystal formation.

"My wife understands what I do and does not ask why I spend so much time in the lab."

What breakthrough allowed you to determine the structure of the β_2 adrenergic receptor?
We finally obtained our first crystals in 2004, but they were too small to be analysed using conventional X-ray sources. I showed pictures of the crystals to Gebhard Schertler, who at the time was helping to develop a microfocus X-ray beamline at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France. We saw the first diffraction patterns at the ESRF in July 2005, confirming that we had a protein crystal. The quality was too poor to determine the 3D structure but the result gave us hope that we could improve the quality of the crystals. My wife joined me for the first experiment at the ESRF that July, and she was the first to see a diffraction pattern, confirming that we had a protein crystal.

Until then I had felt that the project might fail, so I didn't think it was suitable for a student or postdoctoral researcher to work on. Afterwards I recruited two very talented postdocs to join the effort and they succeeded in determining structures of the β_2 adrenergic receptor in 2007 with the help of Stanford colleagues and collaborators from other universities.

How has your wife contributed to your success?
She has been extremely supportive and although she is not a trained biochemist she is very good at finding ways to make the research process more efficient. We met in our first biology class in college and we have worked together ever since, so she understands what I do and does not ask why I spend so much time in the lab.

Were you driven by fear of another group discovering the GPCR structure first?
I had always hoped that someone would get the result, but of course we wanted to be first. We knew there were other groups working on similar projects and there were often rumours that one group or another had crystals. Even as recently as spring 2007, while we were working to obtain the final data for our two structures, there was a detailed rumour that a group in France had the β_2 structure and that a paper had been submitted. That turned out to be false, but it was fortunate for us because it prompted a friend at a Danish pharmaceutical company to donate US$100,000 to our project at a time when things were tight financially.

Did you ever imagine that you might win a Nobel, and what effect it would have?
The first time I really became aware of the prize was in the 1990s when I visited Stockholm while on vacation with my family. We visited the city hall where the ceremony is held and our tour guide described the ceremony. I thought about how exciting it would be, but it never occurred to me that I might win it until 2012, when I found out I'd been chosen. That first year was very disruptive, in part because I accepted too many invitations to speak at conferences and visit universities, often overseas. The volume of e-mail also increased dramatically and as a result I wasn't spending enough time focusing on my research.

Will you continue working in this field?
Yes. There are plenty of challenges ahead in the GPCR field. A crystal structure only gives us a snapshot of the protein in a single state, but these proteins are in constant motion between different states. The role that dynamic behaviour plays in receptor function is of great interest to membrane-protein structural biologists, biochemists, pharmacologists and pharmaceutical-company scientists. There is a lot more work required before we understand how receptors signal to G proteins and other cell-signalling and regulatory proteins such as kinases and arrestins. We also know very little about how receptors work in their native environment: the plasma membrane of living cells. Developing methods to study receptor structure and dynamics in living cells may be even more challenging than crystallographic studies. It will help us to understand the versatile signalling behaviour of GPCRs at a molecular level. By versatile, I mean that one receptor may signal through different intracellular signalling proteins. A better understanding of this behaviour may help us to develop more effective drugs. ■

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