Recognized by the Albert and Mary Lasker Foundation in 1999 for his work in revealing the 3-dimensional structure of the potassium channel, Rod MacKinnon is an odds on favorite to make the transition from Lasker winner to Nobel Prize winner that so many others have achieved. If single-minded determination to answer a scientific question is a requirement for earning the biggest prize in medical research, *Nature Medicine* would put money on MacKinnon.

Rod MacKinnon

Rod MacKinnon wasn't born when A. L. Hodgkin and A. F. Huxley outlined the theory of the nerve action potential in the early 1950s. The idea that ion flux across the membrane of a cell generates the electrical impulses that underpin functions such as the heartbeat, the release of neurotransmitters and thought itself, won the British scientists the Nobel Prize.

Rod MacKinnon

By the time that ion channels next hit the Nobel headlines with Bert Sakman and Erwin Neher in 1991, MacKinnon was himself working as an electrophysiologist in the department of neurobiology at Harvard Medical School. German scientists Sakman and Neher developed the technique of patch clamp recording, a method that allows rapid transmembrane ion exchange to be monitored precisely and shows that the physicochemical changes are mediated via different sets of ion channels in the membrane.

A few years later, MacKinnon decided he was no longer content with electrical recordings to define the potassium channels that he was investigating; he wanted to get a look at the proteins that allow potassium to cross from one side of the cell to another. "I came from an electrical background, and then slowly using molecular biology we identified parts of the potassium channel, but without actually seeing them we knew it would be really impossible to understand how it worked. At that point I made the decision to study X-ray crystallography and to become good at it."

Driven by the idea that seeing is believing, he transferred to Rockefeller University in New York in 1996. "Part of the move was down to the idea that a change in my environment would help me. But when I moved to start afresh, my lab shrunk down to one postdoc plus my wife who was willing to work with me because she felt sorry for me. So this move was a difficult one, all tied in with me deciding to really go after the structure."

His single-minded determination to *see* an ion channel paid off, and in 1998 MacKinnon published the crystal structure of KcsA, the potasium channel of the bacterium *Streptomyces lividans*. For the first time, electrophysiologists could visualize the tiny pores that they had been recording.

Electrophysiology doesn't make for the easiest of cocktail party conversations, and I wondered whether MacKinnon has much trouble discussing his work with nonscientists. I was surprised to hear him say that he thinks most people understand the general concepts of his research, but my skepticism evaporated as he eloquently described the structure of the potassium channel to me.

"Humans are very visual and by just seeing the atomic detail of an ion channel we get a feeling for how it works. When you look at it you can immediately tell what mother nature had in mind. It has a small part around 12Å long near the outside of the membrane which is the selectivity filter [for potassium rather than sodium or calcium] and at the center of the membrane the pore actually has a big swelling in it like a reverse hour glass. Ions like to be surrounded by water, and when you see this swelling you immediately realize that it will hold a lot of water. Another feature is the alpha helices that point straight at the bulging cavity. Looking at this you can immediately understand what the architectural design is—this is the place inside the the oily membranes where an ion would be most unstable because it is furthest from the water, so the structure of the channel brings in a pool of water and these oriented helices provide electrostatic stabilization. What a beautiful design!"

MacKinnon trained as an M.D. at Tufts University in Boston, but with the same focused attitude that enabled him to show the first ion channel to the world, he switched from medicine to science virtually overnight. "I enjoyed my medical training but I was naïve as an undergraduate and didn't understand the difference between medicine and science as a career. I came to realize that medicine uses a different part of your brain to science where its like a puzzle that you have to solve. I like the puzzle solving in science more and I wouldn't be able to do both well so I had to make a choice. I decided that I wanted to do what makes my pulse go up—science."

Since moving to Rockefeller, MacKinnon has become a Howard Hughes Investigator and, in comparison with the early days, has a large team of 14 people working for him. His is still studying the potassium channel and is now looking at voltage-gated proteins rather than the simple, pore-only KcsA channel. Although he says that the team isn't working on the sodium channel—" This is a matter of focus and I don't want to spread to thin"—they have extended their investigations to include calcium and chloride channels. "The calcium channel has a voltage-dependent gate and is in the same general family as potassium, but the chloride channel is a completely different [species]. The real question here is how does nature select a negatively charged ion?"

Despite his intense focus, MacKinnon doesn't like being taken for granted in scientific terms, as he revealed when discussing his move from Harvard to Rockefeller and from electrophysiology to X-ray crystallography. "You know, if you're good at a particular thing, then people have certain expectations of you and the people who come to work with you want to work in the thing you're good at, not in something you don't know about."

So I ask whether being an expert structural biologist now could be a sign that he's ready to move on, and if so, what would he do? He assures me he's not, but that some time in the future he would like to think about something completely new. "I'm quite fascinated by what I read about how biochemical networks and signaling works. Why is a biochemical cell signaling pathway stable? How do the different components interact with each other?"

But such things are, for the moment, only a passing thought. He reverts to his trade of being very focused: "I haven't looked beyond the voltage-sensing problem because that's the way I proceed in taking things one step at a time."

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