

OCTOBER 08, 2003

MacKinnon Wins 2003 Nobel Prize in Chemistry

Roderick MacKinnon, a Howard Hughes Medical Institute (HHMI) investigator at The Rockefeller University, is one of two scientists who were awarded the 2003 Nobel Prize in Chemistry for discoveries concerning channels in cell membranes.

[MacKinnon](#) shared the prize with Peter Agre of the Johns Hopkins University. Agre is currently a member of HHMI's scientific review board. The two scientists were honored for discoveries clarifying "how salts (ions) and water are transported out of and into the cells of the body," according to the Royal Swedish Academy of Sciences.

"This is appropriate recognition for the beauty of MacKinnon's science and the clarity with which he expresses the biological phenomenon," said HHMI President Thomas R. Cech, who won the Nobel Prize in Chemistry in 1989. "MacKinnon's work is exquisite, but he also makes the data come alive with very thoughtful and clear explanations."

"We used mutagenesis for nearly 10 years to study how the potassium channel works without getting the answer we needed."

- Roderick MacKinnon

In 1998, much to the surprise of colleagues, MacKinnon and his colleagues determined the three-dimensional structure of a pore that allows cells to control their intake of potassium ions. By determining the structure of the potassium pore, or channel, MacKinnon and his colleagues at The Rockefeller University had solved a riddle that has perplexed biophysicists for decades: How does a potassium channel admit millions of potassium ions per second, while allowing only one smaller sodium ion to slip through for every 1,000 potassium ions?

The answer is important because potassium channels are part of the apparatus that maintains the normal ionic balance across the cell membrane. In

excitable cells, like those in nerves and muscles, for example, the channels help re-establish the electrical difference between the inside and outside of the cells after excitation. Without potassium and sodium channels, neurons could not generate electrical signals and hearts could not beat rhythmically.

HHMI researchers Yuh Nung Jan and Lily Jan of the University of California, San Francisco were the first to determine the DNA sequence of a potassium channel—the Shaker channel in fruit flies—in 1987. But even with the DNA sequence in hand, which allowed researchers to assign the order of amino acids that make up the Shaker channel protein, it took several years for MacKinnon and his colleagues to figure out which amino acids actually formed the tunnel through which the ions passed. By using a technique called site-directed mutagenesis—painstakingly altering the protein by one amino acid at a time to determine the effects of such changes—MacKinnon's group eventually identified a "signature sequence" of eight amino acids that were key to the channel's function. They also demonstrated that potassium channels must consist of four subunits, each one contributing its signature-sequence amino acids to form a selectivity filter.

But try as they might, the researchers could not use mutagenesis to determine the chemical details of how potassium channels selectively admit potassium ions while excluding other ions. "We used mutagenesis for nearly 10 years to study how the potassium channel works without getting the answer we needed," says MacKinnon. "Ultimately, I knew we just had to see it."

And see it they did. MacKinnon and his colleagues produced large quantities of the potassium channel from a bacterium named *Streptomyces lividans*. Then, they isolated the potassium channel protein in pure form and figured out how to use it to make well-ordered crystals, a prerequisite for determining a molecule's structure.

After bombarding the crystals with x-rays, MacKinnon and his colleagues were able to deduce that the potassium channel is made up of four identical subunits assembled in the shape of an inverted teepee. They found that the wide end of the teepee contains the signature-sequence amino acids, which are arranged to form a tunnel into which an ion must fit precisely in order to enter a cell. If an ion is too large, it cannot fit into the tunnel; if it is too small, it does not enter the tunnel because it cannot align correctly to the tunnel's sides.

When the results were published, they created even more of a stir than when MacKinnon first presented them at the March conference. In a commentary in the same issue of the journal *Science* in which the paper appeared, Clay Armstrong of the University of Pennsylvania School of Medicine called the feat of solving the structure of the potassium channel "a dream come true." A similar commentary in *Nature Structural Biology* by HHMI investigator David Clapham proclaimed "At Last, the Structure of an Ion-Selective Channel."

But MacKinnon and his co-workers did not stop with the bacterial ion channel: They also conducted experiments that showed that the fly Shaker channel is similarly shaped. The researchers determined that an exquisitely specific toxin isolated from scorpion venom binds to the fly Shaker channel and mammalian potassium channels just as tightly as it does to the bacterial potassium channel. Because scorpion toxins are known to fit the channels they block exactly, like a lock and key, this suggests that the bacterial, mammalian and fly channels share the same structure. "It's as if nature settled on one way to make a potassium channel," says MacKinnon.

The potassium channel is only one of a dozen or so proteins that span the cell membrane whose three-dimensional structures have been solved, primarily because it is difficult to amass enough of a given transmembrane protein to make crystals large enough to study.

MacKinnon says he hopes that the bacterial potassium channels will be useful for screening potential new drugs. Two human potassium channels have immediate medical importance: KATP, which is located in the beta cells of the pancreas that secrete insulin, and HERG, which helps the ventricles of the heart recharge so they can contract again. HHMI investigator Mark Keating of Children's Hospital in Boston has linked mutations in *herg* with a disorder called long QT syndrome that can lead to deadly heart arrhythmias. Drugs that regulate the activity of these channels might be useful as treatments for diabetes and in preventing sudden death from long QT syndrome. But many more potassium channels are likely to become targets for drug development in the near future. Diseases such as hypertension and epilepsy, for example, should be treatable through pharmacological control of potassium channel functioning.