

Congratulations to the Team of Dr. Rod MacKinnon, MacCHESS, CHESS, and LNS Staff...

Don Bilderback - CHESS, Cornell University

...for the single most important contribution in 1998 from synchrotron radiation in structural biology: the structure of a K channel. It was cited by Science magazine as one of the breakthroughs of 1998 as “the first physical characterization of the membrane protein responsible for the selective movement of K⁺ into and out of cells”. That work was done at CHESS station A1 with special help from the MacCHESS staff.

“An Electrifying structure. As you read this page, electric signals flash from your eye to deep in your brain, traveling through millions of neurons. Each signal is successfully passed along courtesy of molecules in the cell membrane, “gates” that allow certain ions-but no others-to pour in and out of the cell, spreading the change in electrical potential throughout the cell.

This year, in a landmark discovery that reveals one of the biochemical roots of the nervous system, a New York City team published the three-dimensional structure of one such ion channel-selective for the potassium ion-in a bacterium. This long-awaited finding is a technical marvel that provides new insight into how the nervous system works its magic.

After decades of wondering, electro-physiologists can now understand such riddles as how the potassium channel manages to keep out wrong ions, such as sodium, while shuttling an amazing 100 million potassium ions per second across the membrane. The structure reveals that the ions must pass through a narrow filter, where potassium ions fit snugly and briefly bind to the protein. The slightly smaller sodium ions cannot form this bond, making the filter an energetically unattractive place for them. And there are always at least two potassium ions in the filter, repelling each other just enough to ensure that once in, they quickly make their way out the other end. Membrane proteins are notoriously difficult to crystallize, but this year’s triumph may prompt work on the thousands of other such proteins still waiting.”

From F. Bloom, Editor-in-Chief, *SCIENCE*, Vol 282, 18 December 1998, page 2158. Excerpted with permission from the American Association for the Advancement of Science. Copyright 1998.

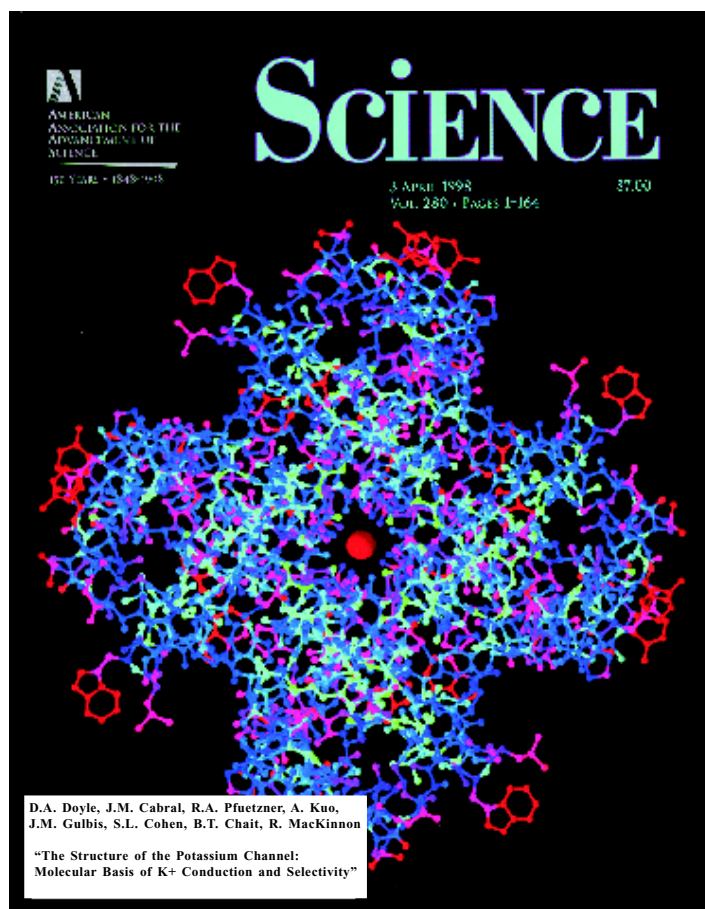


Figure 1: Cover of *Science* containing the report of the potassium channel structure. The potassium ion is the red ball in the center.

Rod MacKinnon and the 1999 Lasker Award

Marian Szebenyi - *MacCHESS, Cornell University*



Dr. Rod MacKinnon

The beginning of the story

In the spring of 1997, CHESS received an Express Mode proposal for time on F-2 from a young doctor, Rod MacKinnon, of the Rockefeller Institute. He did not have a crystallographic background, but was studying the electrophysiology of ion channels. With help from the crystallography group at Rockefeller, MacKinnon had obtained small crystals of the cytoplasmic domain of a bacterial voltage-dependent potassium channel protein, with selenomethionine incorporated, and wanted to try a MAD experiment. He also had some crystals of the native potassium channel, as found in cell membranes. On the MacCHESS feedback form for this first visit, MacKinnon reported “Though our SeMet-containing crystals of the K^+ channel domain were too small to give a successful MAD experiment, we got our first data set on the membrane protein. It is low resolution but a big step forward on our ion channel project. Thank you.”

That visit was the first of many: 8 in 1997, 4 in 1998, 4 in 1999 and 3 so far this year. MacKinnon would come any time - Thanksgiving, Christmas, whatever - always in person, always polite, and soon a knowledgeable crystallographer who knew as much about running the MacCHESS stations as the MacCHESS staff. By early 1998, massive amounts of data had been collected on the potassium channel, in the native and a large number of derivatized forms. The large amount of data, and also a lot of hard work and crystallographic expertise on the part of the Rockefeller group, were needed to solve the complex channel structure. The effort was successful, and MacKinnon reported his results in a cover story in *Science*.

The potassium channel

The membrane of a cell is far from a passive wall; there are many different types of holes in it, each allowing only certain molecules through, often in only one direction, at only certain times. There are many different potassium channels, in different organisms and cell types, which open and close on receipt of different signals. All of them, however, exhibit an extreme selectivity for potassium, in the presence of a high concentration of similar ions such as sodium, as well as a high throughput for potassium (100 million ions per second!). All known potassium channel proteins contain a

“signature sequence” which is identical throughout both eukaryotes and prokaryotes. Hence the potassium selectivity mechanism found in the *Streptomyces lividans* protein studied by MacKinnon’s group is highly relevant to eukaryotic potassium channels. Figure 1(D. Bilderback article on page 19), shows a view down the channel, with a potassium ion in the center. The ions pass through a narrow “filter”, whose precise structure favors binding of K^+ but not the smaller Na^+ . Transit of the potassium ions is possible because there are 3 favorable sites for them in the channel, with easy transfer from one site to the next. Binding a K^+ at one end of the pipe pushes out the ion at the far end; there are always at least 2 ions in the filter.

Recognition

Science cited the structure of the potassium channel as one of the “breakthroughs” of 1998. *Nature*, in September 1999, described the work as “a crucial step forward for this field”. In 1999, MacKinnon received the Albert Lasker Basic Medical Research Award for “elucidating the functional and structural architecture of ion channel proteins, which govern the electrical potential of membranes throughout nature, thereby generating nerve impulses, and controlling muscle contraction, cardiac rhythm, and hormone secretion.”

The continuing story

Rod MacKinnon and his group are not resting on their laurels; they are hard at work on new and even more complex ion channels, and continue to visit CHESS to collect data, both MAD and monochromatic, on weakly diffracting crystals containing difficult but highly exciting and important molecules.