



## Roderick MacKinnon, M.D.

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**Electrical signals play many roles in the body: They control the pace of the heart, regulate the secretion of hormones, and transfer information between neurons. The MacKinnon lab studies the physical and chemical principles of biological electricity with a special focus on the passage of inorganic ions, such as potassium and chloride, across cell membranes.**

Ion channels catalyze the diffusion of inorganic ions down their electrochemical gradients across cell membranes. Even though ions move passively through them, ion channels are sophisticated systems responsible for electrical signaling in living cells, an essential component of many physiological processes. MacKinnon aims to understand the physical and chemical principles of ion channel function.

Like enzymes, ion channels have specific substrates: Potassium, sodium, calcium, and chloride channels permit only their namesake ions to diffuse through their pores. The MacKinnon lab has used mutational analysis to show that potassium channels are tetramers of identical subunits and that specific "signature sequence" amino acids form a selectivity filter that allows only these ions to pass through.

To understand how the selectivity filter conducts potassium ions, the MacKinnon lab determined the x-ray structures of numerous potassium channels, including the KcsA potassium channel at a resolution higher than 2.0 Å, and has proposed a mechanism for their function. His lab has also investigated an ion selectivity by determining the atomic structures of prokaryotic and eukaryotic members of the CLC chloride channel family. Although built on a completely different architectural plan than that of potassium channels, these transport proteins use many of the same basic physical principles.

The diverse members of the potassium channel family have evolved to open in response to specific triggers in their environments. To understand the atomic basis of potassium channel gating, the MacKinnon lab has analyzed the function and determined the structures of several different members of the family. For example, studies of MthK and BK have begun to reveal how the free energy of calcium binding is harnessed to open the pore. In addition, the lab has advanced the understanding of how the inward rectifier Kir2 opens in response to a lipid and Kir3 in response to a G protein by resolving these channels' atomic structures. MacKinnon's group has also determined structures of both archaeobacterial and eukaryotic voltage-dependent potassium (Kv) channels and has posited several fundamentally new ideas about their mechanism.

Recently, his group has begun to study mechanical gating, which underlies sensory detection in touch and hearing as well as basic physiological processes such as cell volume regulation and blood pressure control. MacKinnon and others have observed significant mechanosensitivity in the gating of certain potassium and calcium channels. Now, they seek to understand how mechanical forces elicit electrical signals, and if mechanosensitivity is physiologically relevant in these channels.

For much of this ongoing work, lab members employ cryo-electron microscopy, taking advantage of new, highly sensitive direct electron detectors and other advances. By obviating the need for crystals, this technology has made it possible to determine detailed structures of long-inaccessible channels such as Slo1 and Slo2, Eag1, hERG, KcnQ, and HCN to gain new insights into their function.

### EDUCATION

B.A. in biochemistry, 1978  
Brandeis University

M.D., 1982  
Tufts University School of Medicine

### MEDICAL TRAINING

Residency in internal medicine, 1982–1985  
Beth Israel Hospital, Harvard Medical School

### POSTDOC

Harvard University, 1985–1986

Brandeis University, 1986–1989

### POSITIONS

Assistant Professor, 1989–1992

Associate Professor, 1992–1995

Professor, 1995–1996

Harvard Medical School

Professor, 1996–

The Rockefeller University

Investigator, 1997–

Howard Hughes Medical Institute

Senior Advisor, Kavli Neural Systems Institute, 2016–

### AWARDS

Albert Lasker Basic Medical Research Award, 1999

Lewis S. Rosenstiel Award, 2000

Canada Gairdner International Award, 2001

Peri-UNC Neuroscience Prize, 2001

Nobel Prize in Chemistry, 2003

Louisa Gross Horwitz Prize, 2003

### HONORARY SOCIETIES

National Academy of Sciences

American Philosophical Society

### SELECTED PUBLICATIONS

Tao, X. et al. Membrane protein isolation and structure determination in cell-derived membrane vesicles. *Proc. Natl. Acad. Sci. U.S.A.* 120, e2302325120 (2023).

Falzone, M. and MacKinnon, R. G $\beta$ y activates PIP2 hydrolysis by recruiting and orienting PLC $\beta$  on the membrane surface. *Proc. Natl. Acad. Sci. U.S.A.* 120, e2301121120 (2023).

Mandala, V. and MacKinnon, R. The membrane electric field regulates the PIP2-binding site to gate the KCNQ1 channel. *Proc. Natl. Acad. Sci. U.S.A.* 120, e2301985120 (2023).

Haselwandter, C. et al. Quantitative prediction and measurement of Piezo's membrane footprint. *Proc. Natl. Acad. Sci. U.S.A.* 119, e2208027119 (2022).

Mandala, V. and MacKinnon, R. Voltage-sensor movements in the Eag Kv channel under an applied electric field. *Proc. Natl. Acad. Sci. U.S.A.* 119, e2214151119 (2022).