

CHEMICAL HERITAGE FOUNDATION

RODERICK MacKINNON

The Pew Scholars Program in the Biomedical Sciences

Transcript of an Interview
Conducted by

Andrea R. Maestrejuan

at

Rockefeller University
New York, New York

on

1, 2, and 3 April 1997

From the Original Collection of the University of California, Los Angeles

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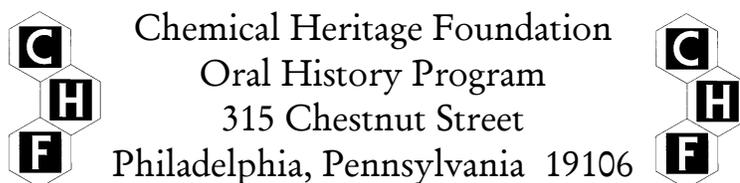
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RODERICK MacKINNON

1956 Born in Melrose, Massachusetts, on 19 February

Education

1978 B.A., Brandeis University

1982 M.D., Tufts University School of Medicine

Professional Experience

Beth Israel Hospital, Boston, Massachusetts
1982-1983 Intern, Internal Medicine
1982-1985 Medical House Officer
1983-1985 Resident

Harvard Medical School, Boston, Massachusetts
1986 Postdoctoral Fellow, Department of Medicine
1989-1991 Assistant Professor, Department of Cellular and Molecular Physiology
1991-1992 Assistant Professor, Department of Neurobiology
1992-1995 Associate Professor, Department of Neurobiology
1995-1996 Professor, Department of Neurobiology

Brandeis University, Boston, Massachusetts
1986-1989 Postdoctoral Fellow, Department of Biochemistry

1996-present Rockefeller University, New York City, New York
Professor, Laboratory of Molecular Neurobiology and Biophysics

Honors

1982 Alpha Omega Alpha, Tufts University School of Medicine
1992 McKnight Scholars Award
1992-1996 Pew Scholar in the Biomedical Sciences
1995 Biophysical Society Young Investigator Award
1997 McKnight Investigator Award

Selected Publications

- MacKinnon, R. and C. Miller, 1988. Mechanism of charybdotoxin block of the high-conductance Ca^{2+} -activated K^+ channel. *Journal of General Physiology* 91:335-49.
- MacKinnon, R. and C. Miller, 1989. Mutant K^+ channels with altered binding of charybdotoxin, a pore-blocking peptide inhibitor. *Science* 245:1382-85.
- MacKinnon, R. et al., 1990. Mapping the receptor site for charybdotoxin, a pore-blocking potassium channel inhibitor. *Neuron* 5:767-71.
- MacKinnon, R. and G. Yellen, 1990. Mutations affecting TEA blockade and ion permeation in voltage-activated K^+ channels. *Science* 250:276-79.
- Yellen, G. et al., 1991. Mutations affecting TEA blockade identify the probable pore-forming region of a K^+ channel. *Science* 251:939-42.
- MacKinnon, R., 1991. Determination of the subunit stoichiometry of a voltage-dependent potassium channel. *Nature* 350:232-35.
- Heginbotham, L. and R. MacKinnon, 1992. The aromatic binding site for tetraethylammonium on potassium channels. *Neuron* 8:483-91.
- Heginbotham, L. et al., 1992. A functional connection between the pores of distantly related ion channels as revealed by mutant K^+ channels. *Science* 258:1152-55.
- MacKinnon, R. et al., 1993. Functional stoichiometry of Shaker potassium channel inactivation. *Science* 262:757-59.
- Root, M.J. and R. MacKinnon, 1994. Two identical noninteracting sites in an ion channel revealed by proton transfer. *Science* 265:1852-56.
- Lu, Z. and R. MacKinnon, 1994. Electrostatic tuning of Mg^{2+} affinity in an inward-rectifier K^+ channel. *Nature* 371:243-46.
- Hidalgo, P. and R. MacKinnon, 1995. Revealing the architecture of a K^+ channel pore through mutant cycles with a peptide inhibitor. *Science* 268:307-10.
- Ranganathan, R. et al., 1996. Spatial localization of the K^+ channel selectivity filter by mutant cycle-based structure analysis. *Neuron* 16:131-39.
- Doyle, D.A. et al., 1996. Crystal structures of a complexed and peptide-free membrane protein-binding domain: molecular basis of peptide recognition by PDZ. *Cell* 85:1067-76.

ABSTRACT

Roderick MacKinnon was born in Melrose, Massachusetts, a suburb of Boston, and grew up in Burlington, an outer suburb of Boston. He is the fourth of seven children. His father had not gone to college, but he picked up computer programming on his own and became a professional programmer. His mother was a substitute teacher as well as homemaker for the seven kids and her husband. MacKinnon was always interested in science, collecting snakes, birds, and other things. Though his parents were observant Roman Catholics, the children attended public schools. After fifth grade MacKinnon went to summer school because they offered a science enrichment program that included giving him a microscope. He loved to look at all kinds of things through that microscope. He remembers his fourth-grade teacher as being good and a high-school science teacher being “inspirational.”

MacKinnon’s first sport was hockey, but after several years he dropped that and turned to gymnastics. He excelled at gymnastics, competing at the state level, being recruited by colleges, and actually considering becoming an Olympic gymnast. Late in his senior year of high school he suddenly realized that he did not want to do gymnastics all his life; luckily he had been in honors classes and his grades were good. He decided to go to the University of Massachusetts in Boston and transfer the next year. He very much enjoyed studying and found that science came easily to him, so he continued his undergraduate work in biochemistry at Brandeis University. He loved the stimulating intellectual climate there.

Unsure what he wanted to do after college, MacKinnon entered Tufts University medical school. He felt all along that he really did not want to practice medicine, that it was not science in the sense he wanted. After finishing his residency he quit medicine and took a postdoc in the lab of Christopher Miller, a professor who had known him at Brandeis. He developed an interest in ion channels, and he learned to play the violin. Here he explains how his childhood interest in understanding natural systems, his interest in problem-solving activities, and his ongoing appreciation for mathematics led to his decision to leave medicine. MacKinnon's willingness to teach himself new techniques and the practice of letting an experiment “speak” to him helped him learn from Miller the artificial bilayer system for studying ion channels.

Observation is important in MacKinnon's experimental method, he says. He began work on charybdotoxin, an ion channel inhibitor, in the Miller lab. Next he describes the Miller lab's efforts to expression-clone a calcium-activated potassium channel and the mutagenesis work required to identify the Shaker potassium channel pore. He found that the active site of a potassium channel is made up of a linear sequence, and he explains the significance of his discoveries.

From there he accepted a position at Harvard Medical School. Deciding to apply a structural biology approach to the study of ion channels, he identified the tetrameric structure of the Shaker potassium channel. Here he talks more about the decision to apply a structural biology approach. He turned down a Howard Hughes Medical Institute position at University of California, San Diego, which he regrets every time he needs to write a new grant proposal. Then his department at Harvard was reorganized. Although things were going well for him at Harvard, he spoke with Torsten Wiesel at a Pew Scholars Program in the Biomedical Sciences meeting and was invited to Rockefeller University to give a talk. He loved Rockefeller and accepted a position there. Then he suffered the difficulties involved in moving a lab. His lab members did not want to leave Harvard, so he was forced to decrease the size of his lab. Miller

warned him about the professional risks involved in focusing on ion channel structure, but MacKinnon likes to “jump in feet first.”

MacKinnon talks about his teaching and research responsibilities at Rockefeller; about recent molecular genetics work that poses new questions about channel structure; the current state of ion channel structure research; his collaborative work with Gary Yellen on potassium channels; and possible collaborations with other scientists. He tells how he began the biochemistry involved in ion channel research with Pew Scholars Program in the Biomedical Sciences funding, and he goes on to discuss his National Institutes of Health (NIH) and McKnight Endowment Fund for Neuroscience grants specifically and NIH support of basic research in general. He explains how one must write grants to meet the different criteria of the individual funding agencies, but he remains committed to his area of interest, despite funding pressures. He extols his wife's, Alice Lee MacKinnon's, ability as a crystallographer. He concludes by discussing the importance of being able to learn new material; the differences in individual styles of learning; the dedication required of MacKinnon's lab personnel; and teaching lab personnel how to do science.

UCLA INTERVIEW HISTORY

INTERVIEWER:

Andrea R. Maestrejuan, Interviewer, UCLA Oral History Program; B.A., History, University of California, Irvine, 1988; B.S., Biological Sciences, University of California, Irvine, 1988; C.Phil., History, University of California, Riverside.

TIME AND SETTING OF INTERVIEW:

Place: MacKinnon's office, Rockefeller University.

Dates, length of sessions: April 1, 1997 (72 minutes); April 2, 1997 (104); April 3, 1997 (82).

Total number of recorded hours: 4.3

Persons present during interview: MacKinnon and Maestrejuan.

CONDUCT OF INTERVIEW:

This interview is one in a series with Pew Scholars Program in the biomedical sciences conducted by the UCLA Oral History Program in conjunction with the Pew Charitable Trusts's Pew Scholars Program in the Biomedical Sciences Oral History and Archives Project. The project has been designed to document the backgrounds, education, and research of biomedical scientists awarded four-year Pew scholarships since 1988.

To provide an overall framework for project interviews, the director of the UCLA Oral History Program and three UCLA faculty project consultants developed a topic outline. In preparing for this interview, Maestrejuan held a pre interview conversation with MacKinnon to obtain written background information (curriculum vitae, copies of published articles, etc.) and to agree on an interviewing schedule. She also reviewed prior Pew scholars' interviews and the documentation in MacKinnon's file at the Pew Scholars Program office in San Francisco, including his proposal application, letters of recommendation, and reviews by Pew Scholars Program national advisory committee members.

For technical background, Maestrejuan consulted J.D. Watson et al., *Molecular Biology of the Gene*. 4th ed. Menlo Park, CA: Benjamin/Cummings, 1987 and Bruce Alberts et al., *Molecular Biology of the Cell*. 3rd ed. New York: Garland, 1994.

The interview is organized chronologically, beginning with MacKinnon's childhood in Massachusetts and continuing through his education at Brandeis University, his medical training at Harvard Medical School, and the establishment of his labs at Harvard and, then, Rockefeller University. Major topics discussed include MacKinnon's research on ion channel structure, his experimental methodology, and funding in the sciences.

ORIGINAL EDITING:

Gregory M.D. Beyrer, editorial assistant, edited the interview. He checked the verbatim transcript of the interview against the original tape recordings, edited for punctuation, paragraphing, and spelling, and verified proper names. Words and phrases inserted by the editor have been bracketed.

MacKinnon reviewed the transcript. He verified proper names and made minor corrections and additions.

Jane Collings, editor, prepared the table of contents and interview history. Beyrer compiled the biographical summary and program staff assembled the index.

TABLE OF CONTENTS

Early Schooling, College, and Medical School	1
<p>Family background. Early schooling. Childhood interest in nature. Participation in hockey and gymnastics. Honors classes in high school. The University of Massachusetts. Moves to Brandeis University. Stimulating intellectual climate at Brandeis. Decision to go to medical school. Learns to play the violin. Empathy with patients in the clinic. Postdoc in the Christopher Miller lab at Brandeis. Develops an interest in ion channels.</p>	
Childhood, Clinical Practice, Postdoctoral Research, and Faculty Years	30
<p>More on family background. More on participation in hockey and gymnastics. Interest in problem-solving activities. Ongoing appreciation for mathematics. Decision to leave medicine. Interest in ion channel research. Learning new techniques. Learns the artificial bi-layer system for studying ion channels. Role of observation in experimental method. Work on charybdotoxin, an ion channel inhibitor, in the Miller lab. The Miller lab's efforts to expression-clone a calcium-activated potassium channel. Identification of the Shaker potassium channel pore. Mutagenesis work required to find the Shaker potassium channel pore. Finds that the active site of a potassium channel is made up of a linear sequence. Significance of findings. Accepts a position at Harvard Medical School. Identifies the tetrameric structure of the Shaker potassium channel. Decision to apply a structural biology approach to the study of ion channels. Accepts a position at Rockefeller University. Difficulties involved in moving a Lab.</p>	
More on Research and Positions Held	61
<p>Researches calcium transient in the James P. Morgan lab at Beth Israel Hospital as a medical resident. Decides not to pursue clinically based research. Moves to the Department of Neurobiology at Harvard. Turns down a Howard Hughes Medical Institute position at University of California, San Diego. Departmental reorganization at Harvard. Teaching and research responsibilities at Rockefeller. Recent molecular genetics work poses new questions about channel structure. Current state of ion channel structure research. Collaborative work with Gary Yellen on potassium channels. Possible collaborations with other scientists.</p>	
Final Thoughts	73
<p>Begins the biochemistry involved in ion channel research with Pew Scholars Program in the Biomedical Sciences funding. National Institutes of Health (NIH) and McKnight Endowment Fund for Neuroscience grants. NIH support of basic research. Writing grants to meet the different criteria of the individual funding agencies. Commitment to his area of interest, despite funding pressures. Alice Lee MacKinnon's ability as a crystallographer. The importance of being able to learn new material. Differences in individual styles of learning. The dedication required of MacKinnon's lab personnel. Teaching lab personnel how to do science.</p>	

INDEX

A

acetylcholine, 49, 76, 82
Africa, 2
Albert Einstein College of Medicine, 49
Alpha Omega Alpha, 27
Anderson, Carol S., 44

B

Bach, Johann Sebastian, 15, 25
Bean, Bruce P., 67
Bergeron, Miss, 6
Beth Israel Hospital, 20, 30, 38, 65, 66
Boston College, 33
Boston Red Sox, 9
Boston, Massachusetts, 1, 2, 4, 5, 6, 7, 9,
11, 12, 17, 18, 20, 26, 33, 38, 54, 69, 70,
78
Brandeis University, 13, 15, 17, 18, 19, 20,
21, 22, 23, 25, 28, 31, 33, 35, 36, 37, 43,
45, 46, 49, 65, 66
Brantz, Howie, 37
Brigham and Women's Hospital, 30, 38
Burley, Steven K., 59, 62, 72
Burlington, Massachusetts, 5, 7, 12, 17
Burlington, Vermont, 7

C

calcium channels, 31, 50, 53
California Institute of Technology, 49, 76
Caltech. *See* California Institute of
Technology
Cambridge, Massachusetts, 2, 66, 67
chaconne, 15, 25, 30, 58
Chan, Michael, 37
Chandy, K. George, 76
charybdotoxin, 41, 44, 45, 46
Choe, Senyon, 76
Cohasset, Massachusetts, 12, 17
Cold Spring Harbor Laboratory, 46, 48
collaboration, 77, 81

Columbia University, 77, 78
competition, 12, 13, 62, 77
Connecticut, 24
Cozumel, Mexico, 58, 78, 79
crystallography, 40, 57, 59, 60, 61, 72, 77,
79
cytochrome oxidase, 76, 82

D

Dallas, Texas, 54
Darst, Seth A., 59, 72
DeLeskey, Kathleen MacKinnon (sister), 2,
33
DNA, 46, 49
Dostoyevsky, Fyodor M., 15, 25, 30
Doyle, Declan A., 60, 61, 62, 87, 88

E

electrophysiology, 41, 56, 60, 78, 80
Europe, 45

F

Fischbach, Gerald D., 59, 70, 71, 72
funding, 1, 79, 80, 81
Furie, Bruce, 24, 25

G

Gadsby, David C., 72
Galilei, Galileo, 23
Germany, 15, 76
Gilman, Alfred G., 54
Gobi Desert, 11
Gouaux, J. Eric, 77, 78
Green, Howard, 68, 69, 70

H

Harrison, Stephen C., 59
Harvard Medical School, 20, 30, 53, 54, 59,
66, 68, 69
Harvard University, 20, 24, 25, 28, 30, 31,
50, 53, 54, 55, 56, 58, 59, 60, 61, 62, 66,

67, 68, 69, 70, 71, 72, 77, 79, 81, 92
Hausdorf, Sharon, 48, 49
Hebrew [language], 50
Heginbotham, Lise, 90
Hess, Peter, 31, 53, 67, 69
Hewlett Packard Company, 55
Hidalgo, Patricia, 90
Howard Hughes Medical Institute, 68, 69,
70, 71
Hudspeth, Albert James, 72

I

ion channels, 30, 38, 39, 40, 41, 45, 56, 57,
58, 60, 67, 73, 74, 75, 76, 77, 79, 80, 81,
82
Irish/Ireland, 2, 4, 9, 19

J

Jan, Lily Yeh, 46, 52, 74
Jan, Yuh Nung, 46, 52, 74
Jewish/Judaism, 19, 23
Johns Hopkins University, 56

K

Kuriyan, John, 59, 62, 72

L

Landsberg, Lewis, 38
Lang, Michael, 81
Leonard, Reid J., 49
Lester, Henry A., 49
leukemia, 2, 27, 37
Lu, Zhe, 90

M

MacKinnon, Alice Lee (wife), 9, 28, 39, 54,
60, 61, 69, 85
MacKinnon, Dennis (brother), 2, 32
MacKinnon, Donald (brother), 3, 33
MacKinnon, Ellen (sister), 2, 27, 32, 33
MacKinnon, Helen Doyle (mother), 2
MacKinnon, Scott (brother), 3, 33
MacKinnon, William (father), 2, 86
Massachusetts, 1, 17, 66

Massachusetts College of Art, 33
Massachusetts Institute of Technology, 24
Max-Planck-Gesellschaft zur Förderung der
Wissenschaften, 83
McKnight Endowment Fund for
Neuroscience, 79, 81
Medical Research Council Laboratory of
Molecular Biology, 76
Melrose, Massachusetts, 1, 7
Michel, Hartmut, 76, 77
Miller, Christopher, 20, 29, 30, 31, 39, 41,
42, 44, 45, 47, 50, 52, 53, 54, 55, 57, 61,
76, 77
MIT. *See* Massachusetts Institute of
Technology
Morgan, James P., 65
Museum of Science, 5

N

National Institutes of Health, 55, 79, 80, 81,
82, 84, 92
New England, 1, 2, 4
New York City, New York, 1, 59, 60, 77,
78, 80, 85, 86
New York University, 78
Neyton, Jacques, 48
NIH. *See* National Institutes of Health
NMR, 56
Nobel Prize, 77
Nova Scotia, Canada, 2
nuclear magnetic resonance, 56

P

Palade, George E., 69, 70
PDZ domain, 60, 79, 82, 87
Pellegrino, Mary MacKinnon (sister), 2, 37
Pew Charitable Trusts, 81
Pew Scholars Program in the Biomedical
Sciences, 1, 16, 35, 43, 55, 58, 59, 62, 77,
78, 79, 84
Pongs, Olaf, 46, 74
pore, 6, 41, 44, 46, 47, 48, 50, 52, 56, 77
potassium channel, 40, 41, 44, 45, 46, 47,
48, 50, 51, 52, 53, 54, 55, 56, 74, 75, 76,
77, 80

Shaker, 46, 47, 50, 52, 54, 56, 74
Pushkin, Alexander S., 15

R

RCA Corporation, 7
Rees, Douglas C., 76
Reinhart, Peter H., 55
religion
 [Roman] Catholic, 4, 9, 19, 23, 63
 Confraternity of Christian Doctrine, 4
Rhode Island, 3
Rhodopseudomonas viridis, 76
RNA, 46, 49, 53
Rockefeller University, 28, 39, 56, 57, 59,
 60, 61, 66, 71, 72, 73, 78, 79, 92
 Laboratory of Molecular Neurobiology
 and Biophysics, 73
Root, Michael J., 90
Russian [language], 6, 12, 14, 15, 17, 25,
 30, 35, 36

S

Salem State College, 33
Salk Institute for Biological Studies, 68, 76
San Francisco, California, 54
scorpion venom. *See* charybdotoxin
Scottish/Scotland, 2, 4
Simon, Sanford M., 72
Somlyo, Andrew P., 54
Springfield College, 17
Stevens, Charles F., 68, 69
Stokes, David L., 78
Swartz, Kenton J., 90

T

Tanouye, Mark A., 46, 74
tenure, 71, 72, 84
tetrameric structure, 55

Torpedo, 76
Tosteson, Daniel C., 68
Tsien, Richard W., 31
Tsien, Roger, 69
Tufts University, 20, 24, 25, 26, 49
Tufts University School of Medicine, 20, 49

U

UCSD. *See* University of California, San
 Diego
UMass. *See* University of Massachusetts
 United States of America, 78
University of California, San Diego, 68, 69,
 70
University of California, San Francisco, 54
University of Massachusetts, 13, 17, 18
University of Pennsylvania, 17
University of Texas Southwestern Medical
 Center, 54
University of Virginia, 54
Unwin, Nigel, 76

W

Walsh, Christopher T., 24, 25
Waltham, Massachusetts, 23
Wang, Da-Neng, 78
Wiesel, Torsten N., 58, 59, 78
Woods Hole Marine Biological Laboratory,
 45

X

Xenopus, 40, 46

Y

Yellen, Gary, 56, 77
Yurow, Gary, 37