RETROSPECTIVE

Frederic M. Richards (1925–2009)

A pioneer of biochemistry and structural biology overturned conceived wisdom about protein structure.

Thomas A. Steitz

Frederic Middlebrook Richards, a world figure in the field of structural biology, died at his home in Guilford, Connecticut, on 11 January at the age of 83. Sterling Professor of Molecular Biophysics and Biochemistry emeritus at Yale, he made seminal contributions to our understanding of protein structure and function, served in an innovative leadership capacity in many organizations, and was a leader in the development of structural biology at Yale.

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In his paradigm-shifting experiment, published in 1958, Fred Richards showed that two fragments of the enzyme ribonuclease A (RNase A) that are separately inactive could be reconstituted to form an active enzyme. During postdoctoral research at the Carlsberg laboratory in 1952, he had demonstrated that the addition of the protease, subtilisin, to RNase A resulted in a cleaved product, RNase S, that remained active. After starting his own lab at Yale, Fred was able to separate the cleaved enzyme into a 20-residue S peptide and a 102-residue S protein, which lacked enzymatic activity. However, when the S peptide was added back to a solution of the S protein, the activity was recovered.

This experiment overturned then current views of protein structure, providing the first evidence that the amino acid sequence of a protein determines the three-dimensional structure it adopts. It anticipated the subsequent discovery that the unfolded whole RNase A protein could be refolded in a test tube to form an active enzyme, a finding that resulted in the award of a Nobel Prize to Christian Anfinsen in 1972—a prize that Richards could arguably have shared. In the 1960s, Richards teamed up with a faculty colleague, Harold Wyckoff, to determine the atomic structure of RNase S, which in 1967 tied with three other proteins as the third protein structure to be established after myoglobin and lysozyme.

Fred Richards was born in New York and obtained his B.S. degree at the Massachusetts Institute of Technology in 1948 and his Ph.D. at Harvard in 1952, working with Barbara Low in the medical school department led by Edsall and Cohen. Thereafter, he pursued postdoctoral research at the Carlsberg laboratory in Copenhagen, Denmark, and at Cambridge University in England. In 1955, he joined the faculty of the Biochemistry Department in the Medical School of Yale University, and in 1963, at the age of 38, he moved to the Science Hill campus at the request of President Kingman Brewster to chair the Biophysics Department, which at the time had a radiological focus. His mandate was to redirect the department to the new field of molecular biology. After a sabbatical at Oxford in 1967–1968, and again at the request of Brewster, he took on the task of merging the Departments of Biochemistry and of Biophysics to form the Department of Molecular Biophysics and Biochemistry.

Fred was an inspiring and charismatic leader, always with a great smile. In his two terms as chair of Biophysics (1963 to 1967) and then Molecular Biophysics and Biochemistry (1969 to 1973), he initiated the development of one of the major centers in the world for the study of biophysics and structural biology, hiring 10 faculty, 7 of whom are now members of the National Academy of Sciences. In doing so he brought together a group of structural biologists that pushed the frontiers of this emerging field.

Fred Richards's most seminal discoveries were often obtained with approaches that were uniquely different from the general direction of the field, and were often executed by himself. While on sabbatical in Oxford in 1968, he constructed a large device employing a half-silvered mirror that greatly simplified the task of fitting atomic models of proteins into experimentally obtained electron density maps. Perhaps because of its unusual construction, it was initially known as "Fred's folly"; but when the rest of the structural biology community found how useful it was, it was respectfully renamed "The Richards optical comparator."

Richards also developed computational methods for understanding the nature, stability, and function of proteins from the knowledge of their atomic structures. His method of calculating their solvent-exposed surface areas has been used ever since to analyze the interactions between proteins and between proteins and ligands. Another of his methods used Voronoi polyhedra to compute volumes occupied by all atoms of a protein and to evaluate the tightness of its packing density. Additional insights into how proteins might interact with ligands large and small were provided by methods developed in his lab to calculate the electrostatic charge distribution on a protein surface, which were used initially to predict how two proteins—flavodoxin and cytochrome c—interact.

Richards was a member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the American Philosophical Society. He took on many tasks that served the community at large, including the scientific directorship of the Jane Coffin Childs Memorial Fund for Medical Research (1976–1991), which awards postdoctoral fellowships, and the presidency of the Biophysical Society and of the now named American Society for Biochemistry and Molecular Biology. He was awarded the Connecticut Medal of Science in 1995.

Throughout his life, Fred had an intense love of sailing, a love shared by Chris Anfinsen (as well as their mutual interest in RNase A). On one occasion, they sailed together from Washington, DC, to Bermuda, and found they had with them only a U.S. road map as a chart. Fred also sailed from New England to England in 1967 on his way to Oxford to spend his sabbatical year in David Phillips's lab. He religiously took at least a month's holiday every August, usually sailing his boat off the coast of Canada with his wife, Sally, and friends (competing with the icebergs). Fred felt that in order to do outstanding science, it was necessary to get away and clear the brain. Fred's passion for making and fixing things using an enormous workshop in his garage enabled him to build a boat he named "Sally's Baarge," reflecting his wife's Maine roots. Fred also had a great concern for the conservation of the environment, both offshore and onshore, and contributed land, time, and effort to the Guilford Land Trust. He is survived by his wife, three children, and four grandchildren.

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