

Don C. Wiley

DON WILEY WAS ONE OF THE PIONEERS WHO TRANSFORMED the specialty once known as “protein crystallography” into the discipline we now call “structural biology.” He helped to create how we picture molecular organization at the cell surface. His two monumental contributions, the structures of influenza virus hemagglutinin (HA) in its various states and the structures of class I and class II major histocompatibility (MHC) molecules in combination with peptides, superantigens and T cell receptors, redefined molecular virology and immunology.

Don and I were recruited by the Harvard Department of Biochemistry and Molecular Biology in 1971. When Don accepted his appointment, a few months after I accepted mine, he came to propose that we set up our laboratories together. He had joined the Harvard faculty immediately upon completing his degree—an unusual step that circumvented the conventional postdoctoral route. The lack of a transitional period within which to find a worthy research goal was the source of considerable stress, as Don recounted in an interview with Sondra Schlesinger (see medicine.wustl.edu/~virology/wiley.htm), but by 1974, he had found a direction that would dominate the rest of his career. He seized upon the study of viral surface glycoproteins—the influenza virus HA in particular—as a route toward unraveling the molecular mechanisms of cell-cell recognition.

Don’s eventual long-term collaborator and friend, John Skehel, had published in 1972 a report on purification and apparent crystallization of HA. Don contacted Skehel in 1974, and in 1976 he spent six months in Skehel’s laboratory in Mill Hill, pushing the HA project forward. They spoke on the telephone at least weekly during the ensuing decades. The HA structure was completed in 1980, and papers describing the molecule and its antigenic properties were published in *Nature* in 1981. It redefined in molecular language the three central properties of the protein—receptor binding, antigenic variation and membrane fusion. Almost overnight, vast areas of virology had become chemistry.

Skehel’s finding in the following year, that HA undergoes a dramatic conformational change at low pH, led to the second phase of work on HA—efforts to define the structural transformations that accompany viral entry. Don regarded the discovery of the low-pH transition as a key moment. For him, “discovery” had a special meaning—not just a completed observation, however important and however hard-won, but rather a qualitative insight, preferably formulated in a few simple sentences, or in a simple drawing.



KAY CHERNUSH

Don’s collaboration with Jack Strominger’s laboratory at Harvard led to an even more celebrated discovery. The HLA major histocompatibility antigen, originally identified as the principal determinant of transplant rejection, was by 1980 known to be a crucial component of the T cell-mediated immune response. Pamela Bjorkman, a graduate student (now an HHMI investigator at Caltech), undertook to crystallize it and to determine its structure. The outcome in 1987 was a turning point in immunology. Various lines of evidence had led to the notion that major histocompatibility molecules like HLA would bind antigen-derived peptides and “present” them on the cell surface. The structure showed how. For sitting between two alpha-helical “rails” on the outer surface of the molecule was the now famous “extra density,” promptly ascribed to bound antigenic peptide.

During the decade and a half since the 1987 paper, Don and his laboratory turned that first glimpse of what the T cell receptor really sees into an entire library of concepts and images. Recognition and prizes came in abundance (the Louisa Gross Horwitz, Gairdner, Lasker and Japan Prizes, to name a few), but Don remained strikingly unaffected by the glamour, his thoughts still fixed on what discoveries might come next. When in the right mood, Don could hold forth at teatime for an hour or more, with his laboratory members (and mine) arrayed around him like iron filings near a magnet. He was a superb mentor of graduate students, and from 1980 to 1992 he chaired the biophysics program that had once granted him a Ph.D.

When Don married Katrin Valgeirsdottir, he learned Icelandic, and Iceland became an adopted second home. He cared very much about his family. He was also deeply conscious of his scientific family—his current and former students and postdoctoral fellows, his collaborators, his mentors. I would wander into his office at the end of almost every day that we were both in town, to talk about our science and to seek or give advice. I will miss those remarkable encounters, just as the rest of Don’s extended scientific family will miss—probably more than any of us yet realizes—his powerful yet unpretentious intellectual presence.

—STEPHEN C. HARRISON

HHMI Investigator, Harvard University

Don C. Wiley joined HHMI in 1987. He died at age 57 in an accident in Memphis on November 16, 2001.