

*At a Meeting of the Faculty of Arts and Sciences on October 2, 2018, the following tribute to the life and service of the late Don Craig Wiley was placed upon the permanent records of the Faculty.*

## **DON CRAIG WILEY**

Born: October 21, 1944

Died: November 16, 2001

Don Craig Wiley was born in Ohio on October 21, 1944, and grew up in New Jersey. As an undergraduate at Tufts University, a research project on electron microscopy of bacterial viruses brought him to the attention of Donald Caspar, who recruited Wiley in 1966 to the graduate program in Biophysics at Harvard, where he chose to conduct his Ph.D. research with William Lipscomb in the Chemistry Department. In 1967, Lipscomb's research team was nearing completion of the first x-ray crystal structure of a protein (carboxypeptidase) to be determined in the U.S. Lipscomb challenged Don with a classic problem—the structure of an allosterically regulated enzyme, aspartate transcarbamoylase (ATCase).

Don quickly became the leader of a small group of students and postdoctoral fellows tackling the ATCase structure, at one point making T-shirts with ATCase in the center of a dead-end maze. By 1971, Don had led the way through it; at that year's Cold Spring Harbor Symposium on Quantitative Biology he burst upon the scene of international protein crystallography with an intermediate-resolution ATCase structure, a freshly granted Ph.D., and a newly acquired sports car. The structural basis of allosteric regulation was a contentious issue in the '70s. Don's work as a graduate student defined the route to an answer.

Don joined the Harvard faculty in the Department of Biochemistry and Molecular Biology (BMB) immediately upon completing his Ph.D., skipping the usual postdoctoral stage. The lack of an intermediate period, during which to find a worthy independent research goal, was the source of considerable stress, as Don was not one to consider a bread-and-butter project to back up his ambitious strivings. Concomitant recruitment to BMB of Stephen Harrison, with whom he shared a laboratory, helped ease the transition. By 1974, Don had found a direction that would dominate the rest of his career, seizing upon viral surface glycoproteins—initially, the influenza virus hemagglutinin (HA)—as a route toward understanding the molecular mechanisms of cell-cell recognition and membrane traffic.

Don chose HA after reading a paper from John Skehel at the National Institute for Medical Research in Britain and promptly arranged to spend a semester in Skehel's laboratory. They formed a remarkable lifelong scientific partnership and personal friendship.

The HA structure was completed in 1980, and back-to-back 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. The deadline for Don's promotion to tenure had come the year before, but fortunately a visit to Don's laboratory allowed Aaron Klug to convince a wise President Bok that the crucial experimental problems had been solved and that important answers would come soon. Bok approved the promotion, even though the key papers were not yet even in draft. Don's promotion enabled him to lead the remarkable Biophysics graduate program upon Arthur Solomon's retirement, which he did until 1992 with great success.

The following year, reference to the HA structure allowed Skehel to show that HA undergoes a dramatic conformational change, acquiring membrane-protein-like properties, under conditions similar to those the virus encounters as it infects a cell. These properties became the key to understanding how HA and proteins on the surfaces of many other viral pathogens initiate infection by membrane fusion. By 1994, Don's group had worked out the details of the conformational change and outlined the membrane-fusion mechanism.

In the late 1970s, Jack Strominger's laboratory managed to purify the HLA major histocompatibility antigen, a crucial component of the T-cell-mediated immune response. Don's progress in studying influenza HA made him the obvious collaborator in an effort to visualize HLA. Pamela Bjorkman, a BMB graduate student, undertook to determine its structure. The outcome in 1987 was a turning point in immunology. Various lines of evidence had led to the notion that proteins like HLA would "present" antigen-derived peptides on the cell surface. The structure validated that notion by revealing the molecular mechanism. Bound between two  $\alpha$ -helical rails on the outer surface of the molecule was an antigenic peptide. Results from many laboratories followed swiftly, characterizing bound peptides and establishing the principles of their incorporation. During the decade and a half following the 1987 paper, Don and his students and postdoctoral fellows, in a continuing collaboration with Strominger, turned this breakthrough in T-cell immunology into a library of concepts and images. He and Strominger shared the 1995 Albert Lasker Basic Medical Research Award,

along with three others; in 1999, they shared the Japan Prize.

In 1987, the Howard Hughes Medical Institute (HHMI) chose to appoint Wiley and Harrison to its new program in Structural Biology, with the proviso that they establish a second laboratory in the HHMI Unit at Boston Children's Hospital. The expansion, in resources and scope, allowed them to undertake even riskier projects, including a joint resolve to contribute to the general effort to understand HIV.

Don served as chair of BMB from 1992 to 1994 and organized the fusion with the Department of Cellular and Developmental Biology, yielding the current Department of Molecular and Cellular Biology (MCB). His most enduring leadership emerged from his scientific charisma. The mesmerizing charm of his hand-drawn lecture slides encapsulated some of his intellectual and personal qualities. At teatime in the laboratory, Don could hold forth for an hour or more, with members of his research group arrayed around him like iron filings near a magnet. At such moments, and at scientific conferences, he had a larger-than-life presence, enhanced by his chiaroscuro affectation of wearing nothing but black or black-and-white.

Don's death in a tragic accident on November 16, 2001, cut short an extraordinary career and left a great gap both at Harvard and in the larger scientific community. He is survived by his wife and their two children, by two children from a former marriage, and by a very large family of "scientific children," whose creativity continues to amplify his intellectual legacy.

Respectfully submitted,

Richard M. Losick

Hidde L. Ploegh

Jack L. Strominger

Stephen C. Harrison, Chair

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