Obituary

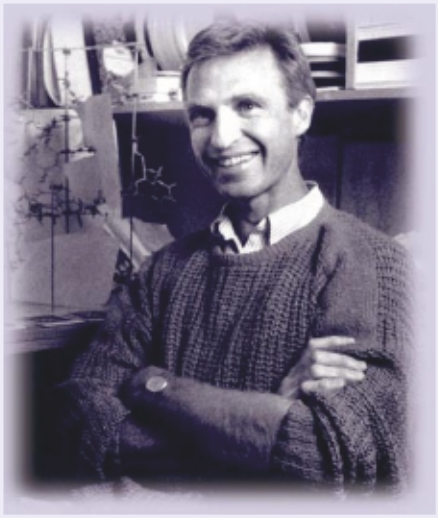
Don Craig Wiley (1944–2001)

The disappearance of Don Wiley, on 15 November 2001 in Memphis, Tennessee, completely mystified family and colleagues. The tragic denouement came with the discovery of his remains in a tributary of the Mississippi on 20 December. His death was ruled an accident.

Wiley was a crystallographer: this is the ultimate molecular biology. One of the twentieth century's greatest discoveries, the structure of DNA, has its roots in X-ray crystallography. In the same vein, the image of a class I MHC protein with its peptide cargo firmly in place will stand as a landmark Wiley discovery that forever changed the field of immunology. Discovered as a set of glycoproteins that are the target of transplant rejection, the products encoded by the MHC (major histocompatibility complex) are now known to alert the immune system to the presence of invaders, such as viruses, through the formation of a complex with snippets of the viral antigens, which is then displayed to patrolling T lymphocytes.

What makes Wiley's work so remarkable is the instant recognizability of the structures solved. Not only can immunologists draw on the back of an envelope the key features of an MHC product, but most virologists can sketch an outline of another of his triumphs — the influenza haemagglutinin protein, a component of the viral membrane or envelope. Asked by a colleague to expound on some biological question, Wiley demurred, saying: "I'm sorry, but I just don't understand anything in biology unless I know what it looks like." There is no better way to express crystallography's credo.

Wiley started his career as a crystallographer in the late 1960s at Harvard University, where he remained. Under the tutelage of William ('Colonel') Lipscomb, he began working on the enzyme aspartate transcarbamylase. Once independent, he turned his attention to the structure of membrane glycoproteins. Through a collaboration with John Skehel of the Medical Research Council labs at Mill Hill, London, a main focus became the structure of influenza haemagglutinins. This collaboration continued until Wiley's death, his stay at Mill Hill leading not only to the acquisition of an Aston Martin in British racing green (mothballed and never used much, as far as I recall), but also to one of the longest and most productive interactions of his career.



STU ROSNER

Crystallographer extraordinaire

The culmination was solving the structure of the full haemagglutinin trimer, which explained much about the structural basis of antigenic variation — the sequence of virus variants that evolve under selective pressure of the host's immune response against it. At the same time, it phrased the key questions for cell biologists studying the entry of the 'enveloped' viruses into animal cells. By 1980, the importance of a mildly acidic pH as the trigger required for virus entry had become part of cell biology lore. The structure of the influenza haemagglutinin trimer and its conformational alterations was the backdrop on which virus entry could now be projected. The drastic changes that accompany the transition of the neutral-pH to the low-pH form of haemagglutinin is a paradigm for the entry of many other enveloped viruses, and bears more generally on our understanding of membrane fusion.

Wiley's mapping work with defined elements of the haemagglutinin trimer provided an elegant demonstration of how one arm of the immune system — antibody defence — operates against viruses. Unveiling the other, the T-cell response, started with discovery of MHC 'restriction' in the mid-1970s. How recognition would be achieved in molecular terms led to a variety of remarkable and detailed proposals, all debunked in the end by the fruit of a long-standing collaboration between Wiley and Jack Strominger — the structure of the soluble portion of a class I MHC molecule known as HLA-A2. This structure revealed the presence of a pocket, occupied by electron density not accounted for by the polypeptide backbone of the class I molecule itself. The pocket holds the antigenic peptide, which is recognized by the receptors of T cells only when firmly bound to the MHC product and presented at the surface of an infected cell. This structure was published in 1987; our concept of T-cell recognition has never been the same since.

Few protein structures explain a biological phenomenon in the way the class I MHC structure does. The biography of Dorothy Hodgkin recounts the first viewing of the insulin structure and the somewhat deflationary response of those invited to inspect it: formidable achievement though it was, insulin's structure did not reveal much about its mechanism of action. The class I MHC structure, by contrast, was a revelation. Wiley's accomplishments were recognized by a Lasker award and the Japan Prize (both shared with Strominger).

Wiley set high standards for himself and others, and shaped the field by training an impressive number of structural biologists, all of whom will do the Wiley legacy proud.

Don Wiley made crystallography fun to the non-crystallographer, too; anyone who heard him speak fell under the spell of his enthusiasm, and his ability to phrase complex biological questions in terms that opened them up for a crystallographic assault. Over the past few years, I would often go to his lab to see whether he was around for a chat — every instance was memorable. Don's enthusiasm for new discoveries would make even the most jaded sit up and take notice. Many will recall also the earlier days: the occasional retreat to the bar of the Hong Kong for scorpion bowls; and his irreverent treatment of the (in)famous Harvard fuddy-duddy establishment, laced with acerbic wit.

In the first half of December I passed through the corridor leading to his shuttered office to find the door open and a bewildered John Skehel at Don's desk, astounded at the level of organization left behind. Of course there is unfinished business, and we cannot say what scientific discoveries we have been deprived of by Don's death. But as a colleague, mentor and friend he is irreplaceable. He leaves behind his wife, Katrin Valgeirsdottir, four children and three grandchildren.

Hidde L. Ploegh

Hidde L. Ploegh is in the Department of Pathology, Harvard Medical School, 200 Longwood Avenue, Boston 02115, Massachusetts 02115, USA.
e-mail: ploegh@hms.harvard.edu