Charles A. Janeway, Jr. 1943–2003

Ruslan Medzhitov

Dr. Charles Alderson Janeway, Jr., passed away on April 12, 2003 at his home in New Haven, Connecticut, after a long illness. With his death, the scientific community lost a truly remarkable scholar, mentor, colleague and friend.

Charlie came from a long family tradition of medical doctors. His great-grandfather was the health commissioner of New York City and his grandfather was the first full-time professor of medicine at the John Hopkins University School of Medicine. His father was the chief of pediatrics at Children's Hospital in Boston.

Charlie was educated at Harvard University, graduating summa cum laude in 1963. He earned his medical degree from Harvard Medical School in 1969. While completing his internal medicine internship at the Peter Bent Brigham Hospital in Boston, he became interested in basic science and particularly in immunology. Charlie trained with Hugh McDevitt at Harvard, with John Humphrey at the National Institute for Medical Research in London, with Hans Wigzell at Uppsala University and with Bill Paul at the National Institutes of Health. In 1977 Charlie came to New Haven to join the faculty at the Yale University School of Medicine. Shortly thereafter, he was appointed an investigator of the Howard Hughes Medical Institute. Charlie was a member of the National Academy of Sciences and the recipient of many awards, including the Yale Bohmfalk award for excellence in teaching. His legendary immunology lectures for Yale medical students formed the basis for his famous textbook *Immunobiology: The Immune System in Health and Disease*, now in its fifth edition.

Charlie was one of the most influential immunologists of our time. He made major contributions to our understanding in several areas of immunobiology, including pathways of T cell development, the interaction of the T cell receptor (TCR) with peptide-MHC complexes, the functions of CD4 and CD8 coreceptors and other accessory proteins, and bacterial superantigens (of which he was codiscoverer) and the molecular mechanisms of superantigen activity. He also made important contributions to the studies of autoimmune diabetes and experimental allergic encephalomyelitis.

Charlie thought big thoughts. His ideas were always distinctively original. There was always something elegant about his ideas, a certain conceptual appeal, a certain something that is hard to explain and probably impossible to learn.

Take the idea of cellular superantigens. Charlie thought that these are host genes, ancestral to viral superantigens, that play a role in T cell development. (Charlie later decided that this hypothesis was wrong, but who is to say that some distantly related host proteins do not play a role in β-selection?) The conformational change in the TCR was another idea of Charlie's, one that was not met with much enthusiasm until the recent proof that the TCR does indeed undergo a conformational change upon ligand recognition. The details of this hypothesis explained how T cells interpret agonist and antagonist peptide ligands. His most recent, and admittedly incomplete, theory provided a fundamental view of the functioning of adaptive immunity. Charlie referred to it as the "self-referential theory of adaptive immunity". Here, the idea was that the TCR complex always recognizes two peptide ligands, one of which is the peptide that the given T cell was selected on in the thymus. If the two peptides are identical, the TCR is not triggered, because the two peptides are by definition self. If the two peptides are different, then one of them has to be foreign because the other peptide is self (assuming that both peptides cannot be self—a reasonable assumption given what we know about the specificity of positive selection). Thus the comparison, or reference, to the limited universe of self peptides allows the T cell to tell if it has encountered a foreign antigen. This 'immunological gestalt' theory sounded pretty far-fetched until recent elegant studies by Mark Davis and Ron Germain demonstrated that self peptides have a fundamental role in T cell activation. Did Charlie get it right? If so, it would not be the first time that he was ahead of his time.

His most original and influential contribution was his work on innate immunity. In his opening lecture at the 1989 Cold Spring Harbor Symposium on Quantitative Biology, Charlie laid out a conceptual framework for the functioning of the innate immune system and its role in the control of adaptive immunity. In retrospect, his insights were truly astonishing. His proposal, which was based entirely on theoretical grounds, was that lymphocyte activation is controlled by the evolutionarily ancient system of innate immune recognition. He suggested that this system would rely on a series of germline-encoded receptors, which he termed pattern-recognition receptors. Furthermore, these hypothetical receptors would have evolved to detect conserved molecular patterns produced by pathogens, but not by their metazoan hosts, thereby endowing the innate immune system with the ability to distinguish 'non-infectious self' from 'infectious non-self'. He further proposed that the mechanism of coupling of innate immune recognition with the initiation of antigen-specific immunity was based on the induction of costimulatory molecules by pattern-recognition receptors expressed on antigen-presenting cells. Finally, he explained that adjuvants function to trigger pattern-recognition receptors, thus mimicking the infectious agents that the system has evolved to recognize.

We now know that these predictions are absolutely correct, and that the principles of pattern recognition apply to all metazoans, whether or not they have adaptive immunity. These principles did not just have an impact on the modern understanding of innate immunity, however. As we are now learning, the pattern recognition theory penetrates all aspects of immunology and provides a unifying fundamental conceptual framework. This is why Charlie's name belongs in the Immunology 'Hall of Fame', along with those of other giants such as Metchnikoff, Erlich and Burnett.

Charlie had an unusually broad knowledge of immunology. He was able to put the dullest results in a broader context, often in an elegant model that motivated further questions and experiments. Charlie loved science. He was a continuous source of inspiration for everyone who trained with him. We will miss the sound of his wooden clogs in the hallways of the Immunobiology Department at Yale, his questions at the seminars, his fervent passion for research and, of course, his proverbial red hat.

Ruslan Medzhitov is in the Section of Immunobiology, Yale University School of Medicine, New Haven, CT 06520-8011, USA. e-mail: ruslan.medzhitov@yale.edu