

Recollections of Charlie: Dr. Charles Alderson Janeway, Jr. (1943–2003)

“...one should always attempt to construct an internal image of the universe of knowledge, and then ask if a given publication can, in any significant way, modify that image” - Charles A. Janeway, Jr. (Presidential Address, AAI, 1998)

I used to comment that it often seemed as though Charlie already knew the answers to the various questions being asked in his lab; it simply was our responsibility to devise the experiments that would provide the necessary data - one might say, the proof of principle. Charlie was a thinker. He rarely embraced the newest or flashiest technology, perhaps he did not always devise the most cutting edge experiments and it could, possibly, be said that he did not always provide the definitive answer to a particular question. But so many times, it seemed, that when an experimental approach brought a question to its conclusion, the data ended up simply proving what Charlie had already been telling us. In fact in some ways, it could be argued that Charlie's greatest impact on Immunology is the seemingly endless stream of incisive review and opinion articles, book chapters and text books that have in some way influenced or shaped the way nearly all immunologists think about various aspects of immunology. Indeed, Charlie's introductory essay to the 1989 Cold Spring Harbor Symposium volume “Approaching the asymptote? Evolution and revolution in immunology” is widely regarded as the seminal contribution that redefined and focused the field of innate immunity.

The Immunologist's Dirty Little Secret. Charlie attributes his early thoughts on innate immunity to insightful questions posed by his wife, Dr. Kim Bottomly, also a world-renowned immunologist. Kim was puzzled by data showing that various effector cytokines were present before their production by effector T cells. Charlie's answer to her question asking where

do these cytokines come from was “I don't know, but has anyone looked at the innate immune system?”. To put a timeframe on this discussion (for us younger immunologists), Pam Bjorkman had recently astounded the community with her crystal structure showing that peptides bound to the cleft of MHC class I and David Schatz and Marjorie Oettinger had just reported the cloning of one of the genes central to adaptive immunity, RAG1.

“(I)n order to obtain readily detectable responses to (protein) antigens” Charlie wrote in this essay, “they must be incorporated into a remarkable mixture termed complete Freund's adjuvant.” “The most likely possibility (to explain this) is that primitive effector cells bear receptors that allow recognition of certain pathogen-associated molecular patterns that are not found in the host. I term these receptors *pattern recognition receptors*.” “I propose that these pattern recognition systems activated effector functions of primitive immune systems before the development of rearranging gene families and continue to play a role in host defense today.” Charlie's prediction that the immune system is dependent upon evolutionarily conserved pathogen pattern recognition receptors was dramatically realized when his lab cloned and characterized the first of these receptors, human Toll (TLR4) in 1997. Did Charlie's words influence the field? A search of PubMed reveals that in 2188 papers the authors refer to “innate immunity” in their abstracts. 2107 of these papers were published after 1989.

Charlie's insights into the field of innate immunity were, however, based on his understanding of the adaptive immune response. His work, for example, demonstrating that CD4 associates with the TCR helped define the concept of coreceptors. Charlie's work also included critical findings and conceptual advances that helped explain superantigens, T cell costimu-



lation and the Th1/Th2 paradigm, as well as work that characterized the peptide cargo presented by mouse MHC class II molecules. Charlie's work on adaptive immunity was largely based upon his interest in understanding how the TCR interacts with MHC. Charlie was fascinated by how TCR interactions with self-peptide:self-MHC during thymic development led to a TCR repertoire that was “self-referential.” In recent work, he also proposed that the B cell repertoire was also self-referential as a result of BCR interactions with self antigens. Understanding the self-referential nature of lymphocytes, Charlie proposed, was critical for understanding autoimmunity and the functions of T suppressor cells.

While Charlie was renowned for speculation, personally he enjoyed the hard facts. I remember explaining to Charlie during our first meeting that I wanted to be a postdoc in his lab because he always seemed to be working on “the big picture.” Charlie replied something along the lines of “seeing the big picture depends upon generating lots of data!”. Indeed, he frequently reminded us that the discussion of a paper might be interesting, but “it's the results section that will be important over time.” Lab members always looked forward to phone calls from Charlie in which he would enthusiastically report the latest findings from whatever meeting he was attending.

There is little doubt, however, that Charlie's favorite data was the identification of human Toll (now called TLR4) and the demonstration that it could induce B7.1 and B7.2 on APCs. So perhaps as you contemplate your data in an effort to construct your in-

ternal image of the universe of knowledge, you will pause and remember "the man in the floppy red hat," Dr. Charles Alderson Janeway, Jr.

Charlie will be deeply missed by his three daughters, Katie, Hannah and Megan, his wife, Dr. Kim Bottomly,

his friends, former trainees, scientists around the world and, unknowingly, by the people he sought to help by understanding the immune system in health and disease.

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