Vincenzo Cerundolo 1959–2020

“Whatever mourns... / Whatever shares / The eternal reciprocity of tears.” —Wilfred Owen

Professor Vincenzo Cerundolo (‘Enzo’), friend and colleague for 32 years, died during the Christmas holidays of 2020. This obituary will be personal, and while I will refer to some of his more spectacular observations, the reader must await the formal memoir from the Royal Society for a full account of his research.

I am going to reflect on Enzo’s time in Oxford in four periods: the first ten years in my lab as a postdoc, the succeeding period as he developed his own group and established new directions in his research, the third period as successful director of the MRC Human Immunology Unit, and finally, the phase of immunological wrestling with the disease that finally vanquished him.

Enzo arrived in my lab in 1988 for what was supposed to be a one-year visit from Italy. He had brought a research problem with him, to which he hoped to apply our recent observations on antigen processing and the definition of T cell epitopes as peptides. The first few months of his research were not rewarding, and it was a lonely time for Enzo, as he had left his new bride Lucy in Italy. One day he came to me, a little disappointed, and asked for my advice. With no hesitation, I advised him to stay in England and work with me. I had noted that Enzo was a craftsman in the lab, and I had no doubt that he had a bright future. We were soon joined by Tim Elliott (whom he called “Teem”) and DPhil student Sebastian Springer, to form the nucleus of my first group.

The first problem Enzo tackled involved the question of how peptides are transported from the cytosol to the endoplasmic reticulum for loading onto class I major histocompatibility molecules. We knew by this time that the epitopes from influenza recognized by cytotoxic T lymphocytes could be defined by short peptides; that transport of the recognized peptides to the cell surface was independent of a formal signal sequence; and, through work on the RMA-S cell line, that the peptide acted as a specific glue to maintain the structure of the class I molecules. We speculated that RMA-S lacked a peptide transporter that might resemble the oligopeptide permease in bacteria, but had no idea where this might be encoded in the genome.

In our reading we had noticed a cell line called .174 that looked superficially like RMA-S. The .174 cells had been produced by radiation mutagenesis, which induced

Credit: Weatherall Institute of Molecular Medicine

large deletions that had been localized to the region of the MHC on human chromosome 6 (rather than the random point mutations seen in RMA-S). Enzo showed that, like the Db and Kb molecules in RMA-S, the HLA-A2 molecules in .174 cells were also stabilized by the recently defined peptide from the influenza M1 protein. This critical result told us that the gene encoding the suspected peptide transporter should lie in the MHC itself. Within a short time, John Trowsdale’s group had identified the RINGs (‘Really Interesting New Genes’) within the deletion, which were similar in structure to oligopeptide permease. This very exciting period culminated in the demonstration by Jonathan Howard’s laboratory in Cambridge that transfections with RING-like homologs from the rat reversed the phenotype of RMA-S.

By 1998 Enzo was naturally keen to start his own group and, particularly, to turn his attention to the T cell response to mutated proteins in cancer cells. The logic was clear: we knew that all cells could process antigens for class I MHC and that virus infection was not required because stably transfected cells processed antigens *in vitro*. One of my favorite papers of his from this time demonstrated the high frequency of A2-restricted cytotoxic T lymphocytes recognizing melanocyte antigens in patients with vitiligo (a disease that causes blanching of the skin). This started his long and profoundly productive investigations into the immune responses to melanoma and other tumors.

Enzo took over the leadership of the Human Immunology Unit in 2010. There are many characteristics of leaders that we all know, but three are underemphasized: a sense of humor, academic humility in the

face of the vastness of our ignorance and a true interest in those one is leading. He had these three ingredients deeply ingrained in his nature. His interest in scientists of all ages as human beings was legendary. It sparked at the Human Immunology Unit Day, where the emphasis was always on the work of younger scientists, and at the yearly sojourn for the group heads at a country hotel, where uninhibited brainstorming while enjoying some good food (and wine) was the order of the day. The sound of laughter permeated these sessions as much as the *grandes pensées*. The one catalyzed the other, of course.

Enzo was at the height of his powers when he received his diagnosis. It was a terrible irony. One hears the phrase “fight with cancer,” but this description is a pale shadow of the intense, personal, grinding immunological battle he waged with the rebellious cells that challenged him. He grappled and wrestled with every resource he could muster at home and from around the world, employing every bit of his deep knowledge and experience. He did this while continuing to lead the unit as if unperturbed, never missing a seminar, always available to his students and colleagues. It was a demonstration of supreme courage.

Behind great people there are usually great families. Lucy, Giulia and Marco were his delight and pride, surrounding and enlightening him with love.

Enzo worked very hard, and one of his endearing quotes from his time in my lab occurred at the end of a long day: “Oh, Alain — I am completely knackerd” (that is, knackered, or exhausted). This has remained part of our laboratory vernacular. Another favorite, said in a reflective mood, “Life is an experiment you can’t repeat.” We will remember Enzo’s particular experiment, with all the power of the eternal reciprocity of tears, as an inspiring example of how it should be done by a master in the art of living. □

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