Alessandro Moretta 1953–2018

On 7 February 2018, at age of 64, Alessandro Moretta passed away after a 7-year fight against advanced lung cancer. The contribution of checkpoint blockade to his long fight is a vivid reminder of the progress and limitations of tumor immunology and immunotherapy, studies to which Alessandro provided important contributions during his career. We mourn the loss of an outstanding scientist, friend and brother. After earning his MD degree at the University of Genoa in 1978, he moved to the prestigious Ludwig Institute for Cancer research in Lausanne as a post-doctoral fellow. Thanks to his important achievements, after a few years, he became the director of the Human Immunology Unit. Returning to Italy in 1988, he was a professor first at the University of Brescia and then at the University of Genoa, as Professor of Histology and Cytology and Director of the Histology Institute. He was also the director of the Center of Excellence for Biomedical Research at the University of Genoa.

Alessandro was a key contributor to immunology. For example, as long ago as the early 1980s, he showed that essentially all T cells can be cloned, a discovery that paved the way for the delineation of T cell diversity and understanding of the type and possible role of T cell infiltrates in immune-system-mediated disorders and infectious diseases. Capitalizing on the high efficiency of his T cell cloning technique, he moved first to γδ T cells and then to investigate natural killer (NK) cells and, at the time, solved the molecular basis of target recognition. The discovery of killer immunoglobulin-like receptors (KIRs) provided an explanation for the missing-self hypothesis of human NK cell function. His ability to unravel the molecular complexity of NK cell–target cell interactions and killing of tumor cells represented a true milestone in immunology. In addition, the monoclonal antibodies to NK cell receptors that he generated have remained invaluable tools for both basic immunology and translational research. At a time when

academic entrepreneurship was not popular in Europe, he cofounded Innate in Marseille, a company that still capitalizes on his tools and discoveries. The impact of the molecules he discovered extends well beyond the NK cell field. For example, his discovery and molecular characterization of natural cytotoxicity receptors, in particular NKp46 and NKp44, have been invaluable for the discovery and delineation of innate lymphoid cells.

Many top-level immunogeneticists were soon attracted to KIR-encoding genes, given their rapid evolution, their chromosomal organization and polymorphism. In this context, on the basis of another discovery by Alessandro—the activating forms of KIRs—it has been possible to define two main categories of KIR haplotypes, A and B. Correlations have been found between the presence of the A or B haplotype and susceptibility or resistance to certain diseases. Alessandro was also a pioneer in studies of the cellular cross-talk between NK cells and various types of innate cells or tumor cells. The NK cell–dendritic cell (DC) interaction revealed an important phenomenon: NK cell–mediated editing of DCs, a mechanism by which DCs that fail to undergo proper maturation are eliminated.

An extremely important translation of his findings, in particular of KIRs and of NK cell alloreactivity, provided the basis for the cure of high-risk leukemia. Hematopoietic stem cell transplantation (HSCT) represents a life-saving therapeutic intervention in acute high-risk leukemia. However, an HLA-compatible donor is found for only 60–70% of patients, which leaves the remaining patients without any efficacious therapeutic options. T cell–depleted haploidentical HSCT was initiated in Perugia (Andrea Velardi's group) and was soon thereafter applied by Franco Locatelli to pediatric patients at Bambino Gesù Pediatric Hospital in Rome. In this transplantation setting, KIR-mismatched alloreactive NK cells serve a central role in anti-leukemia activity without causing graft-versus-host disease. Thanks to Alessandro's supervision, it was possible to carry out selection of the 'best' alloreactive donors. The continuous improvement of criteria for donor selection led to truly unimaginable results, with 70% survival of patients with otherwise fatal diseases. Haploidentical HSCT is now a well-established worldwide reality that has contributed to the saving of thousands of lives of both adult patients and pediatric patients over the past 15 years, a success largely based on Alessandro's discovery.

His fight against disease did not prevent him from pursuing basic and translational research and enjoying life. We remember Alessandro giving lucid scientific talks, despite his breathing difficulties, as well as enjoying life at the seaside or drinking and commenting on a good glass of wine. We will sorely miss his scientific insight and, even more, his smile, wit and irony. ❐

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