Bruno Kyewski 1950–2018

Bruno Kyewski passed away on 22 March 2018. In the midst of dismay and grief for the loss of a mentor and companion in many scientific endeavors, it is comforting to know that Bruno had his wonderful wife Jacky and his son Felix close by his side through the difficult times since he was diagnosed with disseminated prostate cancer in the fall of 2015.

Bruno studied medicine in Bonn and Zurich and obtained his MD degree from the University of Freiburg. After postdoctoral training with Hartmut Wekerle in Freiburg and with Henry Kaplan in Stanford, he became a principal investigator and later head of the Division of Developmental Immunology at the German Cancer Research Center in Heidelberg. Early on, Bruno was fascinated by the idea of taking the thymus to pieces to delineate the functional properties of its stromal compartments. In the late 1970s, this was a daunting task. Bruno rose to the challenge by meticulously perfecting several (by today's standards archaic) cell-separation methods such as '1-g-sedimentation'. His record yields were never matched in the years to come. Indeed, it was the combination of his brilliant and creative mind and supreme dexterity in the *ex vivo* preparation of rare cells that enabled Bruno to reveal fundamental aspects of thymus biology. As a postdoctoral fellow, Bruno showed that thymic dendritic cells were exquisitely efficient in presenting circulating self antigens, whereas cortical thymic epithelial cells, despite their equally abundant expression of major histocompatibility complex (MHC) class II, failed to do so. More than a decade before the discovery of unique antigen-processing machineries in cortical thymic epithelial cells essential for positive selection, Bruno's seminal observation already suggested fundamental differences in the way peptide–MHC ligands are generated for central tolerance on the one hand and positive selection on the other.

After establishing his own laboratory in 1984, Bruno studied the half-life of peptide–MHC class II complexes in various organ microenvironments. The kinetic aspects of antigen presentation received little attention at the time, and the concept of dendritic cell maturation was only beginning to emerge. Bruno observed a considerably longer half-life of peptide–MHC complexes in the thymus than in peripheral organs, which had obvious implications for the induction of

central tolerance. He also bravely ventured into an area that even today remains perhaps one of the most intellectually and experimentally challenging facets of T cell biology: positive selection. Using a bispecific antibody that simultaneously targeted immature thymocytes and cortical thymic epithelial cells, Bruno induced a synchronized wave of T cell differentiation and thereby revealed crucial kinetic features of positive selection.

I joined Bruno's laboratory as a PhD student in 1994. Genetic engineering was revolutionizing immunological research, and models with transgenic expression of T cell antigen receptors had confirmed the longstanding hypothesis that autoreactive T cells can undergo clonal deletion in the thymus. Obviously, this required that the self antigen become 'visible' to developing thymocytes; it was hard to envision how tissue-restricted antigens (TRAs) would meet this condition. Instead, 'peripheral tolerance' was supposed to do the job. Against this background, we set out to study the fate of T cells specific for a unique class of self antigens: acute-phase proteins. Not only are these prototypical liver-specific TRAs, but also their expression oscillates between marginal at steady state and 1,000-fold higher upon induction. To our great surprise, we found that specific T cells were deleted in the thymus, irrespective of whether expression in the liver was 'on' or 'off'. I argued that this was an artifact owing

to ectopic intrathymic expression of our transgenic neo-antigen, yet Bruno, following his remarkable scientific instincts, insisted that we pursue this unexpected finding further. It turned out that intrathymic expression indeed was a physiological feature not only of acute-phase proteins but also essentially of every TRA we examined. We coined the term 'promiscuous gene expression', and Bruno's knack for stromal cell separation once again was instrumental in showing that this phenomenon is a unique feature of medullary thymic epithelial cells. After that fundamental discovery, Bruno continually provided insights into the molecular regulation of promiscuous gene expression and how it supports tolerance induction. His finding that medullary thymic epithelial cells can hand over TRAs to dendritic cells suggested an elegant mechanism by which self antigens that are expressed by only a few hundred cells per thymus can nonetheless efficiently promote central tolerance. Bruno's work shed light on the extent and inter-individual variation of promiscuous gene expression in the human thymus, suggesting that variability in thymic autoantigen expression might constitute a hitherto unappreciated risk factor for autoimmune diseases. Indeed, Bruno and others reported that allele-specific variations in intrathymic expression correlate with disease susceptibility in type 1 diabetes, myasthenia gravis, Grave's disease and autoimmune myocarditis.

Those who had the privilege of getting to know Bruno will remember him as a warmhearted, unassuming and open-minded person. Every so often, he seemed fallen out of time in the most positive sense, enormously knowledgeable and literate far beyond research, driven by genuine curiosity and an enviable ability to marvel at things. Bruno would never be seen blatantly 'selling' a story, and he was always extremely critical with his own work, being the first to point out potential caveats. Writing these lines, I can see Bruno, raising his eyebrows while asking: "Was it all that important?" Sure it was, Bruno; we will sorely miss you. □

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