Benedita Rocha (1949–2021)

It brings great sadness and the deepest regret to convey the news of the death of my friend, colleague and mentor, Benedita Rocha. Benedita passed away on 2 October 2021 after a long fight against lung cancer. Her research focused on the study of T cell physiology, and many of the advances in our understanding of lymphocyte homeostasis and memory can be traced back to her pioneering discoveries.

After earning a medical degree from the University of Lisbon, Benedita performed her PhD work with Maria de Sousa in Glasgow, where she explored the regulatory function of T lymphocytes in immune responses. She then moved to the Medical School of Nova University, Lisbon, where she was appointed Professor of Immunology. In these early days, Benedita hypothesized the existence of regulatory mechanisms that maintain lymphocyte numbers, laying down the foundations for her future work on T cell homeostasis.

In the 1980s, Benedita moved to the Necker–Enfants Malades Hospital in Paris, where she made major contributions to the understanding of T cell physiology. In her adopted city, Benedita interacted with phenomenal immunologists and postulated the existence of peripheral T cell tolerance mechanisms. At the time, the dominant theory indicated that T cell tolerance was solely defined in the thymus, during the differentiation of immature T cell precursors, but Benedita thought otherwise. As such, she joined forces with Harald von Boehmer at the Basel Institute of Immunology, in Switzerland, to investigate whether mature T cells can become tolerized in the periphery. In the early 1990s, the efforts of Benedita and Harald culminated with the demonstration that peripheral tolerance to self-antigens occurs through the elimination of self-reactive T cells and through T cell clonal anergy. This seminal work paved the way for multiple studies on peripheral T cell tolerance and had important implications for autoimmune disease research.

Benedita then continued her quest to better understand lymphocyte homeostasis, focusing on the survival requirements of T cells. She collaborated with António Freitas at Institut Pasteur in Paris, and in 1997 they demonstrated that mature T cells require constant T cell receptor (TCR) signals to survive in the periphery. This pioneering work demonstrated that the survival of peripheral T cells is an active and dynamic process, relying on continuous intercellular interactions via TCR–major-histocompatibility-complex signals. This landmark study would pave the way for the understanding of T cell behaviour in the absence of lymphocyte progenitor supply. Thus, Benedita's work continues to have an important impact in the context of congenital and acquired T cell deficiencies following anti-cancer therapies.

Credit: Dr António Freitas

In the early 2000s, Benedita explored the granularity of peripheral T cell pools further, demonstrating that, following antigen stimulation, naive T cells permanently differentiate to become memory T cells. Benedita demonstrated that memory T cells are endowed with novel properties that ensure increased efficiency on a single-cell basis. At the time, as the identification of clones of naive and memory T cells with the same TCR repertoire in vivo was challenging, these studies were major technical endeavours. By employing combined mutant and TCR transgenic mice, Benedita would go on to circumvent these hurdles and use this strategy to further interrogate the molecular and genetic fingerprints underlying the differentiation of naive T cells into their memory counterparts. To this end, Benedita developed and implemented quantitative single-cell expression assays that would be also used to characterize the heterogeneity of effector T cell subsets during immune responses in mice and humans, notably in the study of the immune response to HIV infection. In parallel, Benedita also characterized the proliferative mechanisms of memory T cells and the cell-cycle strategies that empower memory cells with exceptionally fast and efficient proliferative rates. Finally, she established that the $CD4^+$ T cell 'help' is critical to the generation of efficient cytotoxic memory T cells. Together, these discoveries had a remarkable impact in our understanding of T cell differentiation in vivo and shed light on the mechanisms that underly efficient vaccination protocols.

Finally, and in parallel to these discoveries on peripheral T cells, Benedita also studied extrathymic T cell differentiation. Her work identified unconventional T cells that differentiate in the intestine from immature precursors that migrate from the thymus to the intestine to give rise to natural intraepithelial lymphocytes.

Benedita left behind an enormous body of knowledge and an unconditional love for immunology, but her legacy goes well beyond that. She inspired many colleagues and friends who benefited from her intelligence, focus and sharp sense of humour. Benedita was also mindful of the people around her and their aspirations, and it was with great affection and pride that she supported those she loved the most — her close friends, husband António, daughter Filipa and the greatest love of her most recent years, her grandchildren. She will be sorely missed by all those whose lives, careers and science she touched. ❐

Henrique Veiga-Fernandes ✉
Champalimaud Centre for the Unknown, Champalimaud Foundation, Lisboa, Portugal.
✉*e-mail: henrique.veigafernandes@research.fchampalimaud.org*

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