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Journal club

TRACKING THE T CELL REPERTOIRE

For the first few decades after the identification of T cells and the realization that they do not engage antigen directly, the analysis of specific T cell responses was made extremely difficult by the very low frequency of such cells in the naive repertoire. In 1994, Marc Jenkins and colleagues introduced the use of adoptive transfer of T cell receptor (TCR)-transgenic cells to enable the tracking of antigen-specific T cell responses in tissues in a quantitative manner over time (Kearney *et al.*, 1994). The impact of this superficially simple approach on the field of immunology cannot be underestimated.

This report opened the floodgates for cellular immune studies of enormous variety over the next two decades, all built on the foundation of this adoptive transfer model. In the past 12 years, the approach has been extended to analyse the behaviour of lymphocytes in secondary lymphoid organs and in peripheral sites using two-photon intravital imaging. There are few, if any, major laboratories studying adaptive immunity that have not used this method and, indeed, much of our current understanding of how cell-mediated immunity and B cell–T cell collaboration occur is based on experiments built on this foundation.

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However, after many years of ignoring the unphysiological nature of the high T cell precursor frequency achieved in this manner, many investigators, including Jenkins himself, began to wonder whether T cell responses were distorted by the large number of cells engaging the same ligand. It became clear that intraclonal competition was severely affecting the findings of studies using the adoptive transfer method as originally described. Jenkins accepted the challenge posed by this belated recognition of artifact in the method he introduced and, in a technical ‘tour de force’ that built on tetramer technology, he devised a way to analyse the entire antigen-specific naive T cell pool, even when fewer than 100 such cells were present (Moon *et al.*, 2007).

Thus, Jenkins has come full circle in two seminal papers of the past 25 years: first, by introducing the TCR-transgenic transfer method and, more recently, by devising a new approach that bypasses the central flaw in the transfer method and enables direct evaluation of the T cell repertoire. Many young investigators fail to appreciate just how important technical developments are for gaining new insights into biology. One does not have to design elaborate new machines; real biological insight will do, and Jenkins has shown just how this can be done, and more than once.

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ORIGINAL RESEARCH PAPERS Kearney, E. R. *et al.* Visualization of peptide-specific T cell immunity and peripheral tolerance induction *in vivo*. *Immunity* **1**, 327–339 (1994) | Moon, J. J. *et al.* Naive $CD4^+$ T cell frequency varies for different epitopes and predicts repertoire diversity and response magnitude. *Immunity* **27**, 203–213 (2007)