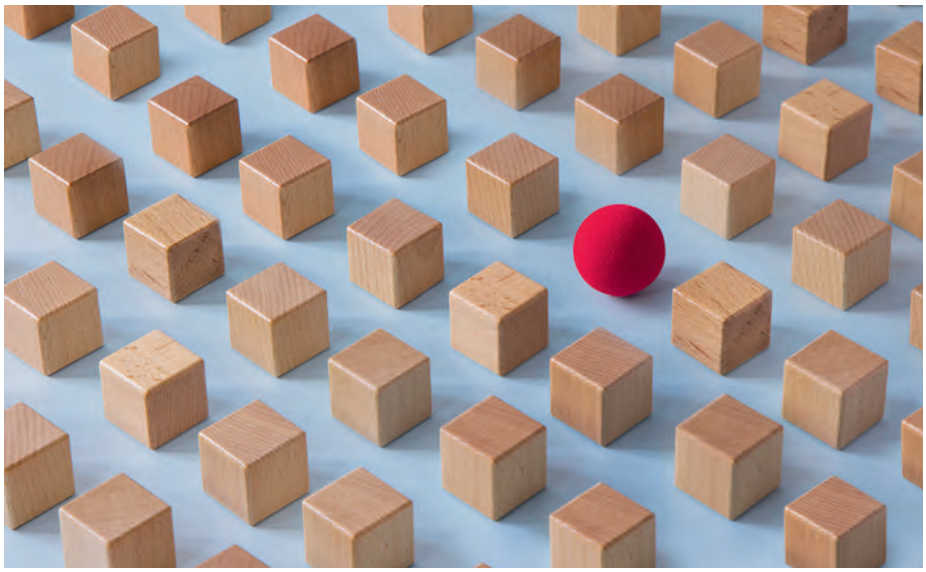
Milestone 14



iNKT cells: defying the definition

By the 1980s, it had become clear that the emerging principles of T cell biology did not apply to all T cell populations — specifically, they did not apply to a group of non-major histocompatibility complex (MHC)-restricted T cells that defied the current dogmas of T cell biology. A number of groups reported cells in mice that had intermediate expression of the αβ T cell antigen receptor and lacked the expression of the defining T cell co-receptors CD4 and CD8. Others reported populations of αβ T cell receptor (TCR)-positive T cells that expressed the natural killer cell marker NK1.1 and initially coined the name 'natural killer T cells' (NKT cells) for these. However, this population of cells was subsequently shown to include a subpopulation that expressed an invariant TCR α-chain, which resulted in their updated rebranding and more accurate definition as invariant NKT cells (iNKT cells).

The paradigm of T cell biology at the time anchored itself to the recognition of peptide antigen presented in the context of MHC class I or MHC class II (Milestone 4). In 1994, Michael Brenner and colleagues reported the recognition of a *Mycobacterium tuberculosis* antigen in the context of the CD1 molecule, which they showed was required for an effective response in this model of infection. Furthermore, this

"a group of non-MHC-restricted T cells that defied the current dogmas of T cell biology"

M. tuberculosis antigen also defied another rule of T cell biology and was shown to be a lipid-based antigen, which suggested CD1 as a lipid-antigen-presenting molecule. Structural studies by Ian Wilson and colleagues, who crystallized CD1d, showed a lipid bound in a network of hydrophobic channels that protruded to the surface of the molecule. Further work from Randy Brutkiewicz confirmed in both mice and humans the role of the MHC class I-like molecule CD1d in the presentation of these atypical T cell antigens. During this time, a team led by Masaru Taniguchi further showed that α-galactosylceramide is also presented by CD1d and identified it as an activating factor for NKT cells. These initial studies were critical in laying the foundation for the identification and characterization of iNKT cells, in addition to the assessment of their role in the immune system and in the context of infection, autoimmunity and cancer.

iNKT cells and MHC-restricted T cells both arise from common lymphoid progenitor cells, and their development occurs in the thymus. However, the development of iNKT cells was found to be somewhat atypical, in that they do not require MHC class II. Progenitors of iNKT cells undergo selection by thymocytes that present lipid antigens in the context of CD1d, and this results in the expression of the master transcriptional regulator PLZF.

Despite their distinct development and mechanism of antigen recognition, iNKT cells mirror MHC-restricted helper T cells and are composed of distinct subsets that resemble the conventional helper T cell lineages. These populations are defined in terms of characteristic cytokines and transcription factors. Analogous to the T_H1, T_H2 and T_H17 cell subsets of helper T cells, iNKT1 cells express T-bet and secrete IFNγ, iNKT2 cells secrete IL-4 and IL-13, and iNKT17 cells express IL-17 and GM-CSF. Additional populations of iNKT cells analogous to follicular helper T cells (Milestone 19) and regulatory T cells (Milestone 15) have also been described and have been shown to have roles in germinal centre reactions and immunomodulation, respectively. Like other immune cells, iNKT cells can navigate the body by the expression of and response to a range of chemotactic receptors and mediators, which allows their localization to tissues (Milestone 7).

The discovery of iNKT cells derived a new paradigm for T cells that are not reliant on peptide and MHC, which paved the way for the recognition of other non-MHC-restricted T cell populations. Understanding of the immunobiology of iNKT cells and their potential applications is in its relative infancy. The roles of iNKT cells in specific disease contexts are emerging, and the use of iNKT cells as a platform for immunotherapy is beginning to be appreciated, with potential impact in a range of immunopathologies, including transplantation, infectious diseases and neuropathology.

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Milestone studies

Beckman, E. M. et al. Recognition of a lipid antigen by CD1-restricted αβ$^+$ T cells. *Nature* **372**, 691–694 (1994) | Lantz, O. & Bendelac, A. An invariant T cell receptor alpha chain is used by a unique subset of major histocompatibility complex class I-specific CD4$^+$ and CD4$^-$8$^-$ T cells in mice and humans. *J. Exp. Med.* **180**, 1097–1106 (1994)

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