

## Outside the box

This Focus on natural killer cells aims to highlight what is currently known and what remains to be understood about these important innate immune cells.

First identified in 1975 by virtue of their ability to rapidly kill tumor cells without previous 'priming', NK cells have puzzled and dazzled—perhaps in equal measures—immunologists for more than 30 years. No longer considered simple 'killing machines', NK cells have gained recognition for their abilities to secrete cytokines that influence the differentiation of adaptive immune responses, to combat viral and parasitic infections, and to promote vascularization of implanting embryos during pregnancy. Like other cells capable of unleashing potentially dangerous inflammatory responses, NK cells can be controlled by regulatory T cells. Yet, in some situations, NK cells themselves exert regulatory function; for example, they can kill 'overstimulated' macrophages, dendritic cells and activated T and B cells. Recent data even indicate that NK cells may, in some situations, 'recall' previous encounters with immunological insults.

In this issue of *Nature Immunology*, we present a Focus on this multi-tasking immune cell lineage. In addition to the articles mentioned below, highlights of recent NK cell research findings, annotated links to papers deemed seminal by experts in the NK cell community, and a selection of important NK cell papers that recently appeared in the pages of Nature Publishing Group journals will be freely accessible online for six months.

For anyone still doubtful that NK cells can do much more than their name would imply, Eric Vivier reviews the evidence ascribing an impressive array of diverse activities to NK cells, which are increasingly appreciated as being composed of phenotypically and functionally distinct subsets. Importantly, Vivier urges immunologists to probe the functions of NK cells in diverse biological situations, so as not to underestimate the importance of this immune lineage. As illustrated by Laurence Zitvogel in a Perspective, whether our ever-expanding understanding of the biological capabilities of NK cells can be successfully translated into clinically efficacious therapies awaits further work, both at the bench, to understand the extent of NK cell cross-talk with other immune cell populations, and in the clinic, to determine whether successful manipulation of NK cell activity might require combinatorial treatment that enhances NK cell effector functions, modulates NK cell trafficking patterns and dampens NK cell suppressors.

Lewis Lanier reviews our current knowledge about the molecular mechanisms through which NK cell responsiveness is regulated. In addition to highlighting the need to incorporate physical and temporal considerations, in addition to biochemical considerations, into future studies of signaling pathways of NK cell receptors, Lanier also illustrates the scope of the progress made since the first proposal that NK cell activity is controlled by inhibitory receptors specific for class I major histocompatibility molecules. Klas Kärre's historical Essay

explains how he conjured up that very proposal, which is now referred to as the 'missing self' hypothesis, while writing his PhD thesis. This hypothesis came about thanks largely to Kärre's open mind, willingness to think 'outside the box' and reliance on empirical evidence.

In a Perspective, Wayne Yokoyama praises this type of mindset, and contrasts it with theoretical biases that have plagued the NK cell field in the past and can be toxic to any type of hypothesis-driven science. As parents sometimes expect younger children that physically resemble older siblings to also display similarities in behavior and preferences, scientists sometimes expect cell types sharing some phenotypic or functional features to resemble each other on all counts. We may never know whether progress in understanding NK cell biology was hampered by experiments designed to reveal T cell-like characteristics of NK cells, or by the unintentional twisting of NK cell data to fit them into a T cell-centric view of the immune system, or even by the transfer of T cell-centric nomenclature to NK cell biology. Nevertheless, Yokoyama highlights strategies—likely to be useful for all biologists, not just those working on NK cells—designed to avoid bias-induced 'traps' in the future, and leads one to wonder what the immunology world would be like had NK cells been discovered before their T cell brethren.

In his Focus Overview, Jim Di Santo proposes a conceptual framework that may be helpful to scientists seeking to answer outstanding questions about NK cell biology. Itself an example of outside-the-box thinking, this framework encourages departure from the concept of NK cells as a static, 'one-size-fits-all' population. Instead, Di Santo suggests that immunologists factor environmental and functional niches into their considerations of NK cell biology. Few immunologists would argue with the premise that NK cells in lymph nodes encounter cellular and molecular forces markedly distinct from those in the uterus. Efforts to embrace rather than ignore the diversity of NK cell populations might actually aid investigations aimed at understanding why so many apparently phenotypically and functionally distinct populations exist, and whether and how these populations may be harnessed for therapeutic benefit.

With this Focus issue, we strive to convey the point that as NK cells themselves likely adapt to different biological situations and micro-environments, immunologists seeking to unravel persistent mysteries of NK cell biology must adapt their thinking and strategies to new NK cell data, much of which might, at least at first glance, seem surprising in light of longstanding dogmas.

We gratefully acknowledge the financial support of Innate Pharma and Novo Nordisk in producing this Focus. *Nature Immunology* takes full editorial responsibility for the content of these pages. 