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NEWS & VIEWS

LEGENDS OF ALLERGY AND IMMUNOLOGY

# Hergen Spits—A legend at the top of his career

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## 1 | MAJOR CONTRIBUTIONS

- Discovery of the role of adhesion and CD3 re-directed killing in T cell–mediated cytotoxicity (from 1980)
- Dissection of the mechanisms of thymic selection in human chimeras (from 1986)
- Elucidation of the role of IL-4 (from 1987) and IL-10 (from 1991) in immunoregulation
- Description of human T-, NK-, and dendritic cell ontogeny (from 1990)
- Immortalization of antigen-specific B cells for clonal production of high-affinity therapeutic antibodies (from 2004)
- Discovery of human innate lymphoid cell (ILCs) subsets, their differentiation and plasticity (from 2009)

Hergen Spits' retirement symposium was held in the Zuiderkerk, Amsterdam, the Netherlands, on 18 February 2019. As the moderator of this symposium, and co-author of this article, Bianca Blom, made a telling analogy between the time-magnitude relationship of Hergen Spits' research career and the adaptive immune response. While Hergen had made enormous impact in his first wave of immune discoveries during 1980–2006, his second wave was even stronger. Indeed, Hergen was using his remarkable memory, generated during his groundbreaking studies of T- and NK cells, to make the paradigm-shifting discovery of several subsets of innate lymphoid cells (ILCs) in humans. By using his wide knowledge and capacity for disruptive and truly innovative thinking, Hergen has cross-fertilized different fields of immunology to make an impressing number of groundbreaking discoveries. That makes Hergen a legend.

### 1.1 | Hergen's first wave of discoveries

Hergen graduated (with honors) in medical sciences at the University of Amsterdam in 1983. During these years, Hergen Spits and his supervisor Jan De Vries (Figure 1A–C) had developed the techniques and tools needed to make fundamental discoveries in human T-cell biology. Hergen discovered the principle of CD3-mediated redirected killing in humans,[1] which is now generally used for bispecific T-cell engager antibodies in cancer therapy and he was the first to demonstrate that non-specific transient adhesion precedes TCR—antigen interaction. The 80 s represented a new era in immunology, with the cloning of the first cytokines and the discovery of Th1 and Th2 cell subsets. In 1985, Hergen left for research in industry. First at Schering Plough, France, where he played a key role in dissecting the immune system in severe combined immunodeficiency (SCID) patients transplanted with fully mismatched hematopoietic stem cells. These pioneering studies in human chimeras paved the way to the discovery of IL-10 producing type 1 regulatory T cells. Later on at DNAX research institute, Palo Alto, USA (Figure 1D), he was a driving force in the early studies of IL-4 and IL-10,[2] and their role in T-cell biology. Hergen's contributions continued in the 90 s, when he returned to Amsterdam and the National Cancer Institute (NKI) and later to the Academic Medical Center (AMC). Here, Hergen described the transcriptional (predominantly inhibitor of DNA binding (Id-) and E-proteins) and molecular


**FIGURE 1** (A–C) Hergen with Jan de Vries, Cox Terhorst (C), and colleagues in 1986 (A), 1993 (B), and 2006 (C). (D) Groups of Hergen Spits, Jan de Vries, Hans Yssel, Rene De Waal Malefyt, Maria Grazia Roncarolo, and Lewis Lanier at the Human Immunology department at DNAX Research Institute in the late 80 s. (E) Lab Christmas party at Hergen's home in 2015

programs governing development of T-, NK-, and dendritic cells (DC) from lymphoid precursors in human liver and thymus. In parallel, Hergen founded the biotech company Impact with Ton Schumacher and Donald Kalff, in 2004 named AIMM Therapeutics, utilizing a B-cell immortalization technique which would eventually lead up to the MedImmune-acquired Nirsevimab, currently in phase 3 clinical trials for respiratory syncytial virus (RSV) infections in infants. Hergen was also a major player in a global effort, supported by the Bill and Melinda Gates Foundation, aimed at developing humanized mouse models for studies of immunity, for example, in vaccine responses. Today such models are greatly aiding our understanding of human immunity. In 2006, Hergen was recruited to Genentech, San Francisco, USA. This was right at the beginning of an era where discovery of the IL-23/IL-17-axis laid the foundation for the description of a new branch of T-cell immunity, initially characterized in mice. It did not take long until Hergen had identified the human Th22 subset.[3] In addition, Hergen quickly realized that the IL-22 production that he observed in the T-cell system had an equivalent among innate lymphocytes resembling NK cells.

## 1.2 | Hergen's second wave of discoveries

Hergen returned to the AMC in 2009. This was an exceptionally exiting time where Hergen, through his life-long contribution in the fields of T- and NK cell development and differentiation, could capitalize on his unique know-how for the discovery of the innate equivalents of T cells, ILCs, in humans (Figure 2A). This work was greatly aided by the pioneering work on lymphoid-tissue inducer (LTi) cells in mice by Reina Mebius and others, eventually leading up to Hergen's and Tom Cupedo's characterization of human fetal LTi cells.[4] Such LTi-like cells, later termed group 3 ILC, could also be found in human mucosal tissues after birth where they provided an innate source of IL-23-induced IL-22. In parallel, Hergen's description of human ILC2,[5] which produce type 2 cytokines, including IL-5 and IL-13 in response to alarmins, such as IL-25 and IL-33, was guided by three landmark papers on the mouse equivalents. Importantly, Hergen's translational discovery filled a knowledge gap for understanding non–T-cell driven (non-allergic) type 2 inflammation in, for example, asthma. Today, multiple drugs targeting the ILC2 pathway show life-changing efficacy for patients with asthma. Similarly, Hergen's discovery of ILC1, provided a source of IFN-γ in the intestine of Crohn's disease patients, where ILC1 were proven to accumulate. Not only did Hergen discover subsets of ILCs, he also described how they develop from naïve precursors, similar to naïve T cells. His most recent contribution to the ILC field was the description of the fantastically plastic nature of ILCs. Hergen and his team (Figure 1E) described the factors that keep lineage stability of ILC2 and ILC3 but also that these cells, if exposed to a specific microenvironment, can acquire features associated with other ILC lineages (Figure 2B).

## 1.3 | Hergen returning to homeostasis

Being very interested in sports, Hergen knows how to make an exit as a true super star. It must be an exceptional feeling to retire when you are at the top of your game. But in the end… did he in fact retire? No, of course not. Hergen continues to supervise students

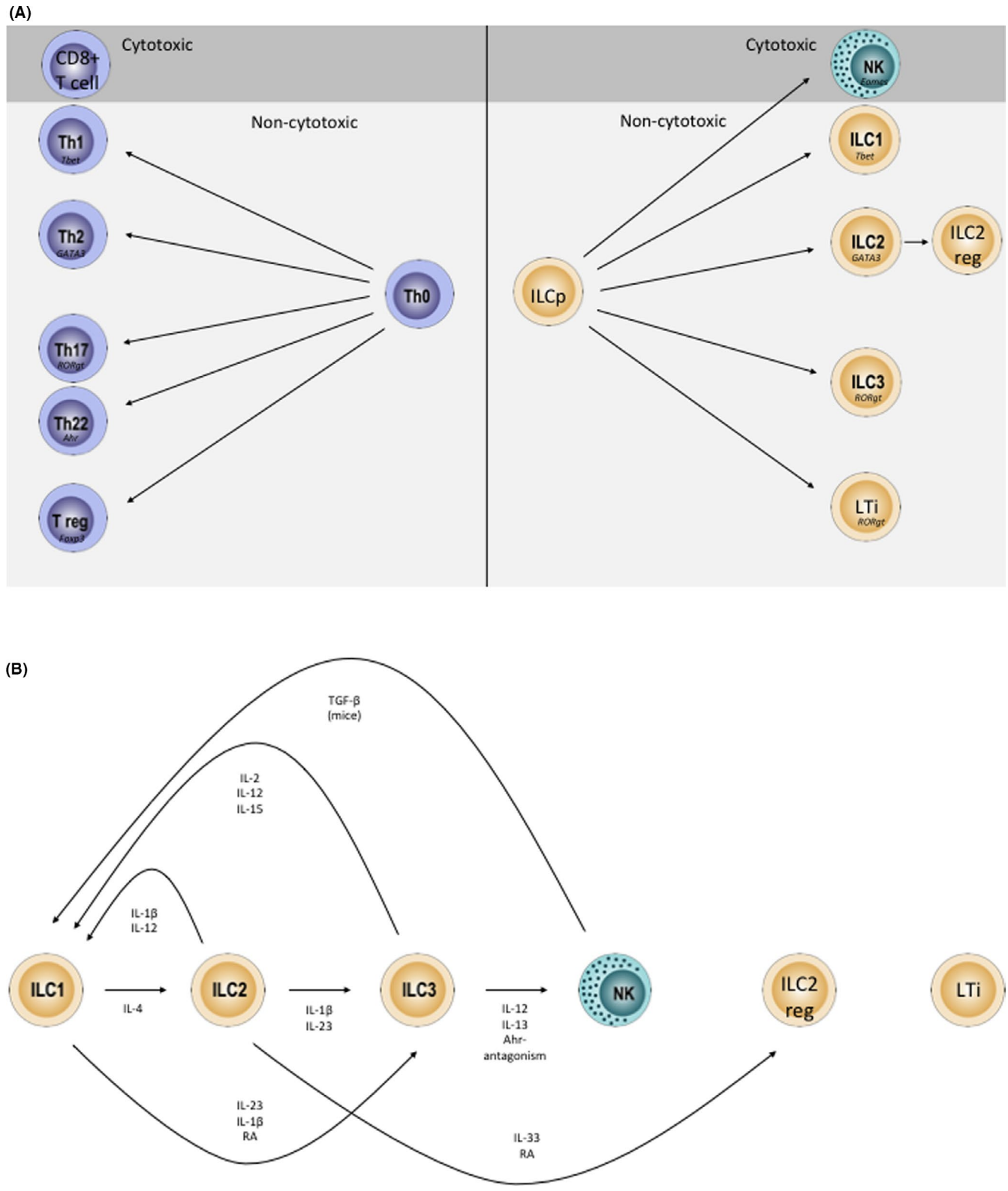


FIGURE 2 Hergen Spits has made groundbreaking discoveries in both T-cell and ILC biology. Following an impressive career of T- and NK cell characterization, Hergen discovered multiple subsets of ILCs in humans and was essential in the realization that (A) the ILC family is a mirror image of the T-cell repertoire in terms of transcriptional requirements and effector functions. Additionally, as has been previously described for T cells, Hergen realized that (B) ILCs are highly plastic and can quickly adapt to the cytokine microenvironment, meeting the prevailing need for tissue immunity without necessarily recruiting additional immune cells. Created with Biorender

and mentor the next generation of excellent scientists at the AMC, Amsterdam, and beyond. Hergen has a never-ending intellectual curiosity, an unbeatable scientific integrity, and an exceptional capability for motivating others. Working with Hergen has been one of the most intense and rewarding experiences of the co-authors lives, shaping our scientific trajectory. But even more important, Hergen has contributed to improving the lives of patients suffering from immune-mediated diseases. We thank him for his contribution and inspiration to generations that will follow.

## CONFLICT OF INTEREST

Dr Mjösberg declares that Hergen Spits is a collaborator and mentor. Dr Blom and Prof Roncarolo have nothing to declare.

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