



Speaker:

**Bernhard Moser**

Henry Wellcome Building  
Dep. of Infection, Immunity and Biochemistry  
School of Medicine  
Cardiff University  
Heath Park  
Cardiff CF14 4XN, UK

Co-authors:

**Marlene Brandes** (Lab. of Immunology, NIAID, Bethesda, MD, USA)  
**Simone Meuter** (Immunology Division, The Walter and Eliza Hall  
Institute of Medical Research, Parkville, Victoria, Australia)

Title: **Some unexpected features about human blood  $\gamma\delta$  T cells**

Abstract

I will discuss several odd features in human blood  $\gamma\delta$  T cells expressing the  $V\gamma9V\delta2$ -TCR. This subset of  $\gamma\delta$  T cells differs from other subsets in terms of their localization (human blood *versus* peripheral tissues) and their antigen specificity. Human blood  $V\gamma9V\delta2^+$  T cells have a memory phenotype and respond to structurally related non-peptide ligands (such as isopentenyl-pyrophosphate [IPP] or hydroxymethylbutenyl-pyrophosphate [HMB-PP]), which do not require processing and presentation by MHC molecules on professional APCs. HMB-PP is an intracellular metabolite produced by many bacteria but not humans or mice. This aspect distinguishes them clearly from  $\alpha\beta$  T cells, whose TCRs have evolved to interact with peptide-MHC class I or class II complexes. Furthermore,  $V\gamma9V\delta2^+$  T cells rapidly secrete cytokines and proliferate during infections with HMB-PP-producing microbes, linking this unique human T cell subset with anti-microbial immunity.

Here we discuss our recent findings of human  $V\gamma9V\delta2^+$  T cells with professional antigen-presenting cell (APC) functions, which we have termed  $\gamma\delta$  T-APCs. Similar to NK cells and monocytes, human blood  $V\gamma9V\delta2^+$  T cells display inflammatory migration properties enabling their immediate recruitment to sites of infections whereas upon activation they start to express the lymph node homing receptor CCR7. In addition, stimulation with IPP or HMB-PP leads to  $\gamma\delta$  T-APCs with professional APC functions, i.e. APCs able to induce the proliferation and differentiation in naïve (antigen-inexperienced)  $\alpha\beta$  T cells. Unexpectedly,  $\gamma\delta$  T-APCs are considerably more efficient than monocyte-derived DCs in antigen cross-presentation, involving the uptake and processing of external antigen followed by the presentation of antigen-derived peptide-MHC I complexes to  $CD8^+$   $\alpha\beta$  T cells. Cross-presentation is essential for mounting cytotoxic T cell responses to infected host cells and tumours. Findings from further investigations into antigen processing by  $\gamma\delta$  T-APCs support their excellent ability to induce  $CD8^+$   $\alpha\beta$  T cell responses to soluble antigens and viruses. Collectively, we propose a model whereby human  $\gamma\delta$  T-APCs, generated at the site of infections in response to microbial HMB-PP, process and present microbial peptides in order to support microbe-specific, adaptive immunity.

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