# In the news

## DRUG-TRIAL DISASTER

A Phase I clinical trial was halted by the Medicines and Healthcare products Regulatory Agency (MHRA, UK) only hours after it began on 13 March 2006, when the six healthy volunteers who were injected intravenously with the drug developed severe clinical symptoms that led to multiple organ failure. Three weeks later, although four of the volunteers have been allowed to go home, one remains in intensive care and another is still in hospital but out of intensive care.

This tragic development has raised many questions, such as what was this new drug? Why did it cause such a violent reaction? And what are the implications for other drugs like it? Some of these questions can be answered quickly and easily, whereas others might take many months (if not longer) to answer.

The drug — TGN1412 — is a CD28-specific superagonist monoclonal antibody developed by TeGenero (Würzburg, Germany) for the treatment of rheumatoid arthritis, multiple sclerosis and leukaemia. The antibody is designed to activate T cells directly, bypassing the normal T-cell activation requirements of signals through both CD28 and the T-cell receptor. In animal tests, TGN1412 activated regulatory T cells — which are a subset of T cells that keep the immune system in check and prevent it from attacking the animal's own tissues — more effectively than other T cells. By preferentially activating this subset of T cells, it was hoped that autoimmunity — which is caused by an immune response to the body's own tissues — could be controlled. So, what happened in these volunteers? As Michael Ehrenstein of University College London, UK, said, "It's possible there was contamination [of the drug]" (*NewScientist.com News Service*, 17 March 2006); it is also possible that there was a dosing error. However, it seems increasingly probable that "the drug may have caused a super-immune response — sending white blood cells called T cells rampaging through the body destroying its own tissues." (*NewScientist.com News Service*, 17 March 2006).

Both the MHRA and the local public prosecutor in Würzburg are investigating the tragic events. However, Thomas Hanke, Chief Scientific Officer of TeGenero, said that the company "observed strict standards for this clinical test" and [in animal studies] "saw no drug related adverse events" (*TeGenero*, 17 March 2006). In addition, a spokesman for Parexel International (Waltham, Massachusetts, USA) — the medical-research company that was running the trial — said, "We believe that best practices were followed and the appropriate policies and procedures were adhered to." (*Nature*, 23 March 2006). So, until we know exactly what went wrong, it seems sensible to adopt the 'softly, softly' approaches suggested by Johannes Löwer, President of the Paul Ehrlich Institute (Langen, Germany): that "research is needed to define better animal models of the human response to CD28 agonists ... [and that] extra precaution [needs to] be taken when antibodies are used to stimulate rather than neutralize components of the immune system" (*Science*, 24 March 2006).

*Karen Honey*

ASTHMA AND ALLERGY

## NKT cells have a role in human asthma

The recently identified subgroup of T cells, CD1d-restricted natural killer T (NKT) cells, have a prominent role in the development of allergen-induced airway hyperreactivity in mouse models of allergic asthma. However, the role of this subgroup of T cells in human asthma has been unclear. Now, a study published in *The New England Journal of Medicine* shows that CD1d-restricted NKT cells do indeed have an important role in human asthma.

Human NKT cells express an invariant T-cell receptor α-chain (TCRα), as well as CD4 or CD8 or neither co-receptor, and are therefore referred to as invariant NKT (*i*NKT) cells. *i*NKT cells respond to glycolipid antigens presented by antigen-presenting cells in the context of CD1d and produce both T helper 1 ($T_H1$) and $T_H2$ cytokines.

To examine the role of these cells in asthma, the frequency and distribution of CD1d-restricted *i*NKT cells in bronchoalveolar-lavage fluid from the lungs of 14 patients with asthma was determined using two methods: flow cytometry after incubation with the monoclonal antibody 6B11 (which is specific for the *i*NKT-cell TCRα) and/or with CD1d-tetramers loaded with α-galactosylceramide (which are also specific for human *i*NKT cells); and reverse transcription PCR of the invariant TCR.

Large numbers of *i*NKT cells were found in the bronchoalveolar-lavage fluid from patients with asthma. Indeed, a high proportion of the $CD4^+$ T cells that were present expressed the invariant TCR, indicating that they were actually *i*NKT cells. Interestingly, these observations seem to be specific to patients with

INNATE IMMUNITY

## RNA viruses: all bases covered?

The cytoplasmic pattern-recognition receptors melanoma-differentiation-associated protein 5 (MDA5) and retinoic-acid-inducible gene I (RIG-I) have both been shown to recognize polyinosinic–polycytidylic acid (poly I:C), which is a synthetic analogue of double-stranded RNA (dsRNA) that is used as a mimic of RNA-virus infection. In addition, RIG-I has been shown to be crucial for the recognition of several RNA viruses, but the function of MDA5 *in vivo* and the relationship between these two receptors *in vivo* were not known. Now, Shizuo Akira and colleagues show that MDA5 and RIG-I recognize different types of RNA virus and are important for host defence against these particular viruses.

To study the *in vivo* function of MDA5, the authors generated MDA5-deficient mice and examined their response, together with the response of RIG-I-deficient mice, to poly I:C. In support of previous (*in vitro*) studies, MDA5 was shown to be crucial for the production of type I interferons (that is, IFNα and IFNβ), an early step in antiviral immune responses. However, in contrast to these previous *in vitro* studies, RIG-I was found to be dispensable for poly-I:C-induced type-I-IFN production *in vivo*. Furthermore, RIG-I was shown to be required for IFNβ production by mouse embryonic fibroblasts (MEFs) in response to *in vitro*-transcribed dsRNAs, whereas MDA5 was not. Taken together, these results indicate that MDA5 and RIG-I can detect different types of dsRNA.

This finding raised the possibility that these receptors recognize different RNA viruses, so the authors assessed the cytokine response of MEFs to single-stranded RNA (ssRNA) viruses (for which dsRNA is a replication intermediate) belonging to various virus families. RIG-I, but not MDA5, was required for the detection of several negative-sense ssRNA

asthma, as the numbers of *i*NKT cells detected in the bronchoalveolar-lavage fluid from patients with sarcoidosis — a multisystem disorder that mainly affects the lungs — were similar to the numbers found in healthy individuals.

The *i*NKT cells from the lungs of patients with asthma produced the $T_H2$ cytokines interleukin-4 (IL-4) and IL-13 but produced very small amounts of interferon-γ. By contrast, *i*NKT cells from healthy individuals or patients with sarcoidosis produced all three cytokines.

Therefore, a subgroup of *i*NKT cells — which express CD4 and produce $T_H2$ cytokines — are recruited to or are clonally expanded in the lungs of patients with asthma and produce cytokines that are essential to the development of this disorder.

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**ORIGINAL RESEARCH PAPER** Akbari, O. *et al.* $CD4^+$ invariant T-cell-receptor$^+$ natural killer T cells in bronchial asthma. *N. Engl. J. Med.* **354**, 1117–1129 (2006)

viruses (including influenza virus) and a positive-sense ssRNA virus, Japanese encephalitis virus (which is a flavivirus). By contrast, MDA5, but not RIG-I, was required for the detection of a positive-sense ssRNA virus, encephalomyocarditis virus (which is a picornavirus). Moreover, RIG-I-deficient mice and MDA5-deficient mice were highly susceptible to infection with the respective viruses, confirming that this receptor-mediated viral recognition has an important role in host defence.

MDA5 and RIG-I are therefore crucial for the recognition of different groups of viruses. How these receptors detect different viral RNAs remains unclear, and the authors suggest that analysing the crystal structures of the helicase (RNA-binding) domains of these proteins might shed light on the molecular mechanisms of this differential recognition.

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**ORIGINAL RESEARCH PAPER** Kato, H. *et al.* Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. *Nature* 9 Apr 2006 (doi:10.1038/nature04734)

T CELLS

# BLIMP1 increases its control over lymphocytes

The transcriptional repressor B-lymphocyte-induced maturation protein 1 (BLIMP1) is the 'master regulator' of the terminal differentiation of B cells into plasma cells. However, two papers published recently in *Nature Immunology* now report that BLIMP1 also has a key role in regulating T-cell homeostasis and activation.

Although the function of BLIMP1 in B cells has been well characterized, the function of BLIMP1 in other cell types has not been studied in detail. To address this gap in our knowledge, Kallies *et al.* generated BLIMP1-reporter mice, in which expression of a bicistronic DNA construct expressing the genes encoding green fluorescent protein (GFP) and a non-functional form of BLIMP1 was 'knocked in' to the gene encoding BLIMP1 (*Prdm1*). Mice homozygous for this construct lack BLIMP1 function and die *in utero*; therefore, subsequent analysis in this study was carried out using recombination-activating gene 1 (RAG1)-deficient mice reconstituted with fetal-liver cells from the knock-in mice (denoted $Prdm1^{gfp/gfp}$ mice). By contrast, Martins *et al.* generated mice lacking BLIMP1 expression only in cells of the T-cell lineage (denoted CKO mice).

Both groups observed lymphocytic infiltration of the colon, lungs and liver, and tissue destruction indicative of colitis in the colon of their mice. Consistent with this inflammatory phenotype, $CD4^+$ T cells from these mice produced more interferon-γ than control cells when stimulated *in vitro* and the total number of effector $CD4^+$ T cells was increased in the spleen and lymph nodes of both $Prdm1^{gfp/gfp}$ and CKO mice. Furthermore, analysis of GFP expression in $CD4^+$ T cells from the $Prdm1^{gfp/gfp}$ BLIMP1-reporter mice and *Prdm1* mRNA in $CD4^+$ T cells from wild-type mice indicated that among $CD4^+$ T cells, effector cells expressed the highest levels of BLIMP1. Evidence that the phenotypes of colitis and an expanded effector $CD4^+$ T-cell population were a result of BLIMP1 having an intrinsic T-cell function (that is, an intrinsic role in regulating T-cell homeostasis) was provided by several observations. First, naive $CD4^+$ T cells from CKO mice, but not $Prdm1^{gfp/gfp}$ mice, hyperproliferated when stimulated *in vitro* under sub-optimal conditions. Second, effector $CD4^+$ and $CD8^+$ T cells from $Prdm1^{gfp/gfp}$ mice hyperproliferated when stimulated with CD3- and CD28-specific antibody in the presence of cytokines. Last, co-transfer of wild-type and $Prdm1^{gfp/gfp}$ $CD4^+$ T cells to RAG1-deficient mice resulted in the preferential expansion of the $CD4^+$ T-cell population lacking functional BLIMP1.

Colitis and expanded effector $CD4^+$ T-cell populations are also characteristics of mice lacking $CD4^+CD25^+$ regulatory T ($T_{Reg}$) cells. However, both $Prdm1^{gfp/gfp}$ and CKO mice had $T_{Reg}$-cell populations, and these cells were functional in *in vitro* assays of regulatory function. By contrast, although $T_{Reg}$ cells from $Prdm1^{gfp/gfp}$ mice showed normal regulatory function *in vivo*, $T_{Reg}$ cells from CKO mice had impaired regulatory function *in vivo*.

Although several points remain to be clarified (including defining the molecular mechanisms by which BLIMP1 mediates its effects in T cells, more precisely defining the $T_{Reg}$-cell phenotype in the absence of BLIMP1 and determining whether BLIMP1 has a role in T-cell development in the thymus), these two studies define a previously unknown function for BLIMP1 as a key regulator of T-cell homeostasis and activation.

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**ORIGINAL RESEARCH PAPERS** Martins, G. A. *et al.* Transcriptional repressor Blimp-1 regulates T cell homeostasis and function. *Nature Immunol.* 26 Mar 2006 (doi:10.1038/ni1320) | Kallies, A. *et al.* Transcriptional repressor Blimp-1 is essential for T cell homeostasis and self-tolerance. *Nature Immunol.* 26 Mar 2006 (doi:10.1038/ni1321)