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

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