## IN THE NEWS

**HIV on the increase in UK**

There has been a 20% increase in new diagnoses of HIV infection in the UK between 2002 and 2003, according to recent figures from Britain's Health Protection Agency (HPA), which monitors infectious diseases. New diagnoses in heterosexuals have risen by 27% in the same period, with most infections contracted outside of the UK in countries with a high rate of infection with HIV. The HPA believes that increases in unsafe sex are thought to underlie these figures. "People must be encouraged to take responsibility for their own sexual health," said Dr Barry Evans from the HPA (HPA).

The increase in rates is also thought to be related to an increase in other sexually transmitted infections, which might influence the transmission of HIV. Nick Partridge of the UK advocacy group, The Terrence Higgins Trust, has urged the UK government to take action — "Modernizing sexual health services … would be a major step forward in helping to tackle this crisis" (The Terrence Higgins Trust). Deborah Jack from the National AIDS Trust (NAT) said, "The messages of the 1980s are as relevant today as they were then. All sectors of the community need to understand the need for safer sex…" (NAT). According to the HPA Chairman Sir William Stewart, "these are worrying data and worrying trends … [a problem] that places a huge additional burden on the NHS [National Health Service]" (HPA).

*Elaine Bell*

ANTIGEN PRESENTATION

# Shocking stimulation

**Heat-shock proteins (HSPs), in addition to their known housekeeping roles as chaperones, can stimulate an immune response to bound antigenic cellular peptides. This response is thought to have two components: stimulation of an innate response through pro-inflammatory, adjuvant effects on dendritic cells (DCs), and the delivery of antigen for crosspresentation on DC MHC class I molecules to induce an adaptive CD8$^+$ cytotoxic T lymphocyte (CTL) response. How efficient is the response and what is the relationship between these two components?**

**Using an assay that measures the ability of antigen-pulsed DCs to generate an effector CTL response, Paul Lehner and colleagues showed that only a small number of human DCs pulsed with influenza-A-derived peptides bound to mycobacterial HSP70 are necessary to induce an efficient antigen-specific CTL response (T-cell:DC ratio of 5000:1). Pulsing DCs with the same peptides in the absence of HSP70, even in the presence of a known DC activator such as lipopolysaccharide, was not effective, and CD8$^+$ T cells could not be stimulated by peptide–HSP70 complexes alone. Therefore, both DCs and HSPs are crucial for the response.**

**Next, they measured the affinity of peptide binding to HSP70 and used this to calculate that 120 pM HSP70-bound peptide can generate a CTL response *in vitro*, whereas a 2000-fold higher concentration of free peptide was unable to do so. The low concentration of mycobacterial HSP-bound peptide and the small number of stimulated DCs required for a CTL response without additional adjuvants in this human system requires further investigation as a potential vaccination method.**

**To determine the minimal HSP70 requirement for generation of a peptide-specific CTL response, the authors created truncated HSP70 proteins containing the known carboxy-terminal peptide-binding domain only. After taking slight differences in binding affinity into account, such mutant forms of HSP70 were as efficient as full-length HSP70 at generating CTLs, indicating that they were able to both stimulate and deliver peptide to DCs. By contrast, an HSP70 mutant with markedly decreased peptide-binding affinity, owing to a point mutation in the peptide-binding domain, could still induce the production of pro-inflammatory cytokines by DCs but did not lead to CTL generation, and therefore the delivery of antigen can be separated from DC stimulation. This mutant HSP70 was unable to generate CTLs even in the presence of excess free peptide, which shows that to be crosspresented, the peptide must be bound to HSP. However, when the concentration of wild-type peptide–HSP70 was limiting, addition of excess mutant HSP70 that cannot bind peptide did enhance the CTL response. So, the two components of the response can be delivered by separate HSP molecules, indicating that other HSPs might be able to enhance the response to a low concentration of peptide-bound HSP in physiological situations.**

*Kirsty Minton*

### References and links

**ORIGINAL RESEARCH PAPER** MacAry, P. A. *et al*. HSP70 peptide binding mutants separate antigen delivery from dendritic cell stimulation. *Immunity* **20**, 95–106 (2004)

**FURTHER READING** Srivastava, P. Role of heat-shock proteins in innate and adaptive immunity. *Nature Rev. Immunol.* **2**, 185–194 (2002)