IN THE NEWS

Cancer vaccine success
An experimental vaccine is proving effective at protecting against cervical cancer and genital warts, according to a new study published in *The Lancet Oncology* (Reuters).

The vaccine — Gardasil — is being developed by Merck & Co., and it targets four strains of human papillomavirus (HPV): HPV16 and HPV18, which are associated with ~70% of cervical cancers; and HPV6 and HPV11, which cause genital warts. Worldwide, cervical cancer affects approximately half a million women each year, and of these, about half will die (Associated Press). The Merck trial involved ~500 women from Brazil, the United States and Europe, half of whom received the vaccine. The trial participants were then tested for HPV infection and lesions or genital warts during a 2.5-year period. According to Dr Luisa Villa of the Ludwig Institute for Cancer Research in Brazil, "If [larger] Phase III studies demonstrate the vaccine is as effective as this, I'm sure that it will change the history of cervical cancer" (Reuters).

A rival vaccine — Cervarix — that targets the two strains of HPV that are associated with cervical cancer is being developed by GlaxoSmithKline and is at a similar stage of development. "The race is on. There is not much to choose between these vaccines. In practice both have proved to be extremely effective", said Dr Anne Szarewski, a clinical consultant at Cancer Research UK (The Daily Telegraph, UK). Both vaccines are expected to reach the market within the next two to three years.

Elaine Bell

IMMUNE REGULATION

Co-stimulation with TIMs

Two papers published in the May issue of *Nature Immunology* provide insight into the function and specificity of the newly identified TIM (T-cell immunoglobulin domain and mucin domain) family of proteins and highlight their role in regulating T-cell responses.

The TIM gene family has eight members in mice and three in humans, all of which are predicted to encode transmembrane proteins that have an IgV domain, a mucin-like domain and a cytoplasmic tail. Umetsu *et al.* focused their studies on the function of TIM1, whereas Meyers *et al.* sought to elucidate the role of TIM4 in the immune system.

Using a monoclonal antibody specific for mouse TIM1, Umetsu *et al.* first showed that TIM1 was expressed by activated T cells and by T cells cultured in T helper 2 (T_H2)-cell-polarizing conditions, and it was absent or present at low levels in resting T cells and T_H1 cells, respectively. By contrast, Meyers *et al.* showed that TIM4 was not expressed by T cells but was expressed by antigen-presenting cells, with the highest expression levels by mature dendritic cells of the lymphoid lineage. To identify the ligand for TIM4, Meyers *et al.* generated a TIM4-immunoglobulin fusion protein. The fusion protein specifically bound activated (but not resting) B and T cells, which led the authors to propose that the TIM4 ligand could be TIM1. To confirm this, they showed that the TIM4 fusion protein bound TIM1-expressing cells, and conversely, a TIM1 fusion protein bound TIM4-expressing cells but not untransfected cells or cells expressing other TIM-family members. Moreover, consistent with the TIM1 expression pattern described by Umetsu *et al.*, the TIM4 fusion protein showed a higher level of binding to activated T_H2 cells than to T_H1 cells.

Next, both groups sought to determine the effect of TIM1 ligation using either the TIM1-specific antibody or the TIM4 fusion protein. *In vitro*, TIM1-specific antibody increased the proliferation of CD4⁺ T cells stimulated with antibodies specific for CD3 and CD28. It also increased cytokine production by T_H2 cells but had no effect on T_H1 cells, which do not express TIM1. T cells from T-cell-receptor-transgenic mice treated with TIM1-specific antibody and primed with the cognate antigen had increased levels of both basal proliferation and proliferation in response to antigen exposure *in vitro*. These cells also produced more interferon- γ , interleukin-4 (IL-4) and IL-10. Similarly, Meyers *et al.* showed that *in vivo* administration of the TIM4 fusion protein increased proliferation of primed T cells, with or without antigen re-stimulation. In addition, *in vivo* ligation of TIM4 by administration of the TIM1 fusion protein increased *in vitro* T-cell proliferation and promoted the production of T_H2 cytokines in favour of T_H1 cytokines, which would usually be produced in the mouse model used.

Finally, Umetsu *et al.* showed that treatment with TIM1-specific antibody could break tolerance to inhaled allergen and promote the development of airway hyper-reactivity after allergen challenge, which is consistent with the identification of *Tim1* as an asthma-susceptibility gene.

Lucy Bird

References and links

ORIGINAL RESEARCH PAPERS Umetsu, S. E. *et al.* TIM-1 induces T cell activation and inhibits the development of peripheral tolerance. *Nature Immunol.* **6**, 447–454 (2005) | Meyers, J. H. *et al.* TIM-4 is the ligand for TIM-1, and the TIM-1–TIM-4 interaction regulates T cell proliferation. *Nature Immunol.* **6**, 455–464 (2005)