In the news

T-CELL VACCINE FOR MS

Following the promising results of a multiple sclerosis vaccine trial in a small group of patients, a large-scale trial has been initiated to test the efficacy of a personalized T-cell vaccine in patients with multiple sclerosis.

The vaccine, known as Tovaxin by its developers, the Texas-based company PharmaFrontiers, is now to be tested in 100 patients with multiple sclerosis. David McWilliams, of PharmaFrontiers, told *BBC News* that "if earlier results were replicated in this study, it might be possible to slow or even halt the progress of the condition." (8 March 2006).

The vaccine is made from the patients' own T cells, which are cultured in the laboratory in the presence of myelin antigens that are targeted by T cells in the disease and irradiated before being returned to the patient. The hope is that an immune response is triggered against the injected myelin-reactive T cells, thereby priming the patient's immune system for elimination of the disease-causing cells. "If that's the case, the earlier we can [vaccinate] after diagnosis the better", McWilliams told *New Scientist* (9 March 2006).

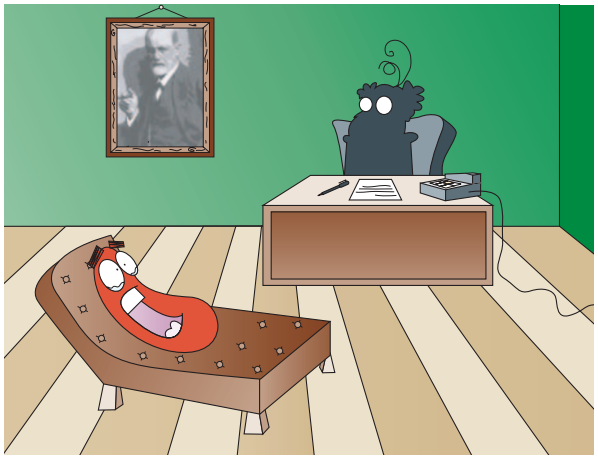
However, Richard Rudick of the Mellen Center for Multiple Sclerosis Treatment and Research in Cleveland, Ohio, is cautioning against over-enthusiasm for the new vaccine as "None have worked so far. This one may, but we don't know yet." (*Guardian*, 9 March 2006). In addition, there is no guarantee that normal T cells will not also be eliminated following vaccination.

Nevertheless, good news might await multiple sclerosis sufferers as the US Food and Drug Administration is expected to lift its ban on prescribing natalizumab (Tysabri; Biogen Idec/Elan). Natalizumab works by blocking the migration of myelin-reactive cells to the brain, and it has been recently reported to be better than existing interferon-β treatments (*The New England Journal of Medicine*, 2 March 2006).

Lucy Bird

REGULATORY T CELLS

Getting down to the specifics



It is now becoming clear that naturally occurring $CD4^+CD25^+$ regulatory T (T_{Reg}) cells not only keep self-reactive T cells in check but also hamper efficient control of microbial infection. However, whether the role of T_{Reg} cells in infection results from specific recognition of foreign antigen or from bystander activation through self-antigen remains a matter of debate. Now, Yasmine Belkaid and colleagues show for the first time that T_{Reg} cells can respond specifically to microbial antigens.

In earlier work, this group showed that, after infection of mice with the parasite *Leishmania major*, T_{Reg} cells accumulate in the skin and draining lymph nodes, where they impede effector-T-cell-mediated clearance of the pathogen. To assess the specificity of these T_{Reg} cells, the authors tested the ability of the cells to proliferate *in vitro* in response to *L. major*-infected bone-marrow-derived dendritic cells (BMDCs). Surprisingly, most of the $CD4^+CD25^{hi}$ T cells isolated from the skin-draining lymph nodes of chronically infected mice proliferated under these conditions. These $CD4^+CD25^{hi}$ T cells were indeed T_{Reg} cells (and not activated $CD4^+$ effector T cells, which also express CD25) because they were shown to express the T_{Reg}-cell-specific marker

T-CELL MEMORY

Less is more

Protective immunity to pathogens requires memory T cells that survive for many years after initial exposure to the infectious agent. The identity of the factors that influence the maintenance of naive and memory T cells *in vivo* remains highly sought after and is the subject of a recent study by Marc Jenkins and colleagues published in *Science*. They show that clone size markedly influences the survival of naive T cells and their memory-cell progeny.

To study *in vivo* T-cell survival, the authors first tracked polyclonal naive $CD4^+$ T cells after adoptive transfer to congenic recipients. Although most of the two million transferred cells died within the first 2 months, with an estimated half-life of 50 days, 10% of the cells were still detectable a year after transfer. However, when one million monoclonal naive $CD4^+$ T cells from T-cell receptor (TCR)-transgenic (DO11.10) mice were transferred to histocompatible mice, the half-life of these cells was only 12 days.

The authors proposed that the poor survival rates of monoclonal- compared with polyclonal-cell populations might be related to clone size. To enable the

forkhead box P3 (FOXP3) and, in response to *L. major*-infected BMDCs, they secreted the regulatory cytokine interleukin-10 (IL-10) and only small amounts of the effector-T-cell cytokine interferon-γ. Moreover, the $CD4^+CD25^{hi}$ T-cell population suppressed *in vitro* proliferation and cytokine release by activated $CD4^+CD25^-$ T cells in an antigen-dependent manner.

Next, the authors carried out experiments to rule out the possibility that the proliferation of T_{Reg} cells from the infected mice was caused by exposure to microbial products or nonspecific activation. They showed that T_{Reg}-cell proliferation was abolished when the cells were exposed to BMDCs that lacked MHC class II molecules or to BMDCs that were activated with lipopolysaccharide and CD40-specific antibody, confirming that the T_{Reg}-cell response was antigen dependent.

Consistent with the dependence of T_{Reg}-cell function on *L. major* antigen, they showed that, unlike memory T cells, T_{Reg} cells did not spread to organs in which the parasite was absent but remained in sites of persistent infection. In addition, in mice that were treated to clear the pathogen completely, T_{Reg} cells responding to *L. major*-infected BMDCs could not be detected. This compartmentalization of T_{Reg}-cell function might be an important mechanism for avoiding systemic immunosuppression by these cells.

Finally, the authors generated T_{Reg}-cell lines from *L. major*-infected mice. Transfer of these cells to chronically infected mice caused a marked reactivation of disease, which was also associated with marked expansion of the transferred T_{Reg}-cell line. This proliferation was antigen specific because it was not seen when the T_{Reg}-cell line was transferred to uninfected mice or mice infected with *Toxoplasma gondii*.

These observations have important implications for our understanding of the role of T_{Reg} cells in chronic infections, such as with HIV or hepatitis C virus, and might help us to design strategies to specifically target these cells during infection.

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ORIGINAL RESEARCH PAPER Suffia, I. J., Reckling, S. K., Piccirillo, C. A., Goldszmid, R. S. & Belkaid, Y. Infected site-restricted $Foxp3^+$ natural regulatory T cells are specific for microbial antigens. *J. Exp. Med.* 13 Mar 2006 (doi:10.1084/jem.20052056)

detection of low numbers of seeded cells following transfer of just 1,000 monoclonal cells, they developed a cell-enrichment method using magnetic beads. Of the 1,000 naive DO11.10 cells that were transferred, 10 cells survived with a half-life of 50 days and 80 cells survived with a half-life of 104 days. This is similar to the half-life of polyclonal naive $CD4^+$ T cells, indicating that when present in physiologically appropriate numbers, naive monoclonal T cells survive longer and proliferate more.

Next, the authors showed that clone size also influences antigen-driven proliferation of naive $CD4^+$ T cells. When high numbers (approximately 10^5) of naive DO11.10 cells were transferred, the cells divided fewer than 8 times and increased in number by 20-fold to a peak 3 days after injection of the cognate antigen. As observed in the absence of antigen, these cells declined rapidly, with a half-life of 11 days. However, when only 100 naive DO11.10 cells were transferred, the cells divided more than 8 times and increased in number by 200-fold after antigen exposure. Moreover, the ensuing memory population consisted of 1,500 cells with an average half-life of 46 days. So, like naive cells, memory cells benefited from a low initial clone size.

To explain these results, the authors suggest that individual $CD4^+$ T-cell clones compete for TCR recognition of the limiting peptide–MHC-class-II ligand, rather than for a survival factor such as interleukin-7. This intraclonal competition among naive T cells might maximize both the diversity of the T-cell repertoire and the longevity of memory cells generated from this repertoire.

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ORIGINAL RESEARCH PAPER Hataye, J., Moon, J. J., Khoruts, A., Reilly, C. & Jenkins, M. K. Naive and memory $CD4^+$ T cell survival controlled by clonal abundance. *Science* 2 Mar 2006 (doi:10.1126/science.1124228)

IN BRIEF

INSECT IMMUNITY

Downregulation of the *Drosophila* immune response by peptidoglycan-recognition proteins SC1 and SC2.

Bischoff, V. *et al. PLoS pathog.* **2**, e14 (2006)

The function of peptidoglycan-recognition proteins (PGRPs) that have amidase activity, such as PGRP-SC1 and PGRP-SC2, in *Drosophila* spp. is not clear. To examine the role of these proteins *in vivo*, PGRP-SC-deficient flies were generated using RNA interference. One of the two distinct signalling pathways involved in antimicrobial host defence in *Drosophila* spp., the IMD (Immune deficiency) signalling pathway, is over-activated in these mutant flies following bacterial challenge. Activation of the IMD pathway is also increased in larvae with reduced levels of PGRP-SC1 and PGRP-SC2 after feeding on *Escherichia coli*, compared to wild-type larvae. These mutant larvae are highly susceptible to infection and have higher mortality rates, caused by over-activation of the IMD pathway. Therefore, this study indicates that PGRPs with amidase activity have an essential role in dampening the IMD pathway, thereby controlling the intensity of the response to bacteria in *Drosophila* spp. and preventing bacteria-induced larval death.

REGULATORY T CELLS

Toll-like receptor 2 controls expansion and function of regulatory T cells.

Sutmuller, R. P. M. *et al. J. Clin. Invest.* **116**, 485–494 (2006)

The mechanism by which intrinsic $CD4^+CD25^+$ regulatory T (T_{Reg}) cells are controlled is not fully understood. Recent studies have shown that Toll-like receptors (TLRs) are expressed by T_{Reg} cells. This study shows that engagement of TLR2, but not TLR4 or TLR9, on T_{Reg} cells resulted in the proliferation of these cells both *in vitro* and *in vivo*. This proliferation was accompanied by a temporal abrogation of the suppressive function of the T_{Reg} cell. Transfer of TLR2-sufficient T_{Reg} cells into TLR2-deficient mice inhibited the immune response to *Candida albicans*, whereas co-administration of a TLR2 ligand resulted in the loss of the suppressive effect of the T_{Reg} cells and reduced fungal outgrowth. Therefore, the temporal abrogation of T_{Reg}-cell-associated suppression by TLR2 signalling allowed for an increased antifungal response, indicating an important link between TLRs and T_{Reg} cells in the control of an immune response.

IMMUNOTHERAPY

Interleukin-15 rescues tolerant $CD8^+$ T cells for use in adoptive immunotherapy of established tumors.

Teague, R. M. *et al. Nature Med.* **12**, 335–341 (2006)

The eradication of tumours by $CD8^+$ T cells is often impeded by the fact that T cells are tolerant to most tumour antigens. To find ways to overcome this tolerance, the authors used a mouse model, in which T-cell-receptor-transgenic T cells are tolerant to a candidate tumour antigen transgene that is expressed in the liver. In response to antigen, the transgenic T cells failed to proliferate or form stable immune synapses *in vitro*, although they showed cytolytic activity when stimulated *in vivo*. Further studies showed that treatment of the tolerant T cells with interleukin-15 (IL-15) could rescue all effector functions *in vivo*, including proliferation. Importantly, transfer of IL-15-treated tolerant T cells to mice bearing established tumours caused complete tumour eradication in 50% of the mice, indicating that IL-15 could be used to enhance tumour immunotherapy.