thermogenesis[11]. The possible effects of diabetic neuropathy on autonomic regulation of adipose tissue have not been mentioned in recent reviews[10], but in light of the findings of Bartelt *et al.*[5] and others[4,11], these effects may now attract more attention.

Bartelt *et al.*[5] have provided a provocative, landmark mechanistic study in BAT biology. Moreover, their results may shed light on the puzzling connection that has been observed between CD36 variants and body mass index, the metabolic syndrome and dyslipoproteinemia[12]. Through the uptake and incineration of TRLs, activated globules of brown fat may substantially improve obesity, insulin resistance and vascular health in humans.

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Tuberculosis vaccines—a new kid on the block

Stefan H E Kaufmann

New tuberculosis vaccines are urgently needed to reduce the threat of this devastating disease. An approach consisting of a fusion protein of three tuberculosis antigens provides significant protection in before- and after-exposure challenge mouse models, representing a crucial step forward in tackling tuberculosis in latently infected individuals (pages 189–194).

Today, tuberculosis is still a major health threat, and *Mycobacterium tuberculosis* (*Mtb*) is responsible for more human deaths than any other microbe. This may seem surprising, because tuberculosis can be cured by antibiotics, and a live vaccine composed of the attenuated agent of bovine tuberculosis (*Mycobacterium bovis*), Bacille Calmette-Guérin (BCG), is also available.

However, these intervention measures are insufficient for several reasons. First, BCG only reliably protects against tuberculosis in newborns and fails in adult pulmonary tuberculosis, the most prevalent form. Second, tuberculosis therapy requires three or more drugs given over a six-month period, and poor compliance with this regimen has led to increased resistance. Third, the rise in HIV infection and consequent immune suppression have driven tuberculosis resurgence. One key feature of *Mtb* is its ability to persist in a dormant state, and an estimated 2 billion individuals are latently infected with *Mtb*. Only 10% of these people develop disease, with tuberculosis reactivation typically occurring after weakening of immunity, such as after HIV infection.

One of the most promising approaches to control tuberculosis is the development of new vaccines, and a dozen vaccines are currently in clinical trials[1]. These candidates have been tested as preexposure vaccines and afford superior protection against tuberculosis compared to BCG in animal models, but none can achieve sterile eradication—the complete elimination of *Mtb* from an infected individual (**Fig. 1**).

In this issue of *Nature Medicine*, Aagaard *et al.*[2] show that a new subunit vaccine, H56, which combines two tuberculosis antigens expressed early in infection and one expressed during latency, can stimulate a host T cell response to all three vaccine components. H56 has several impressive features—it protects mice when used to boost BCG and offers significant protection on its own in both the before-exposure and after-exposure settings. This latter quality is particularly crucial, as this shows that a tuberculosis vaccine can stimulate a T cell response in the face of dormant *Mtb*, allowing H56 to confer superior protection compared with BCG (**Fig. 1**).

H56 is a fusion protein comprising two well-known vaccine antigens of *Mtb*—antigen 85B (Ag85B) and 6-kDa early secretory antigenic target (ESAT6)—which the authors[2] combined with a new antigen, Rv2660c, in the adjuvant CAF01 (ref. 3). Ag85 cognates are shared by *Mtb* and BCG and therefore are true booster antigens, but ESAT6 is only present in *Mtb* and is not a true booster antigen. The function of Rv2660c is unknown, but it is induced by *Mtb* during starvation[4]. Aagaard *et al.*[2] showed that Rv2660c was highly expressed throughout *Mtb* infection in mice and was hence a universal antigen that represents metabolically active and dormant *Mtb*. In contrast, Ag85B and ESAT6 were only highly expressed in early Mtb infection.

The single components of H56, the H56 fusion protein and another fusion protein vaccine, H1, which is composed of Ag85B-ESAT6 in CAF01 (this vaccine was previously developed by the same group and is currently in phase 1 clinical trials), were compared with respect to their efficacy and capacity to induce type 1 T helper cytokine secretion. Interferon-γ (IFN-γ) is considered the central cytokine in the control of tuberculosis, and recent findings suggest that multifunctional $CD4^+$ T cells producing IFN-γ, tumor necrosis factor-α (TNF-α) and interleukin-2 (IL-2), may be key in long-term protection[5] (**Fig. 1**). H1 alone induced marginal protective immunity but boosted BCG. In contrast, H56 produced long-term protection that was comparable to or slightly better than BCG, suggesting that Rv2660c is crucial for the improved protection of H56 over H1. H56 protective activity was accompanied by the appearance of multifunctional T cells but, interestingly, BCG did not induce multifunctional T cells, despite its substantial protective effects. Hence, the issue of the relevance of multifunctional T cells in protective immunity against tuberculosis and their value as correlates of protection remains open.

Mouse models reflect active tuberculosis disease but not latent infection, as after low-dose aerosol infection *Mtb* establishes itself in the lung at a high burden of ≥1 million bacteria, which cause disease.

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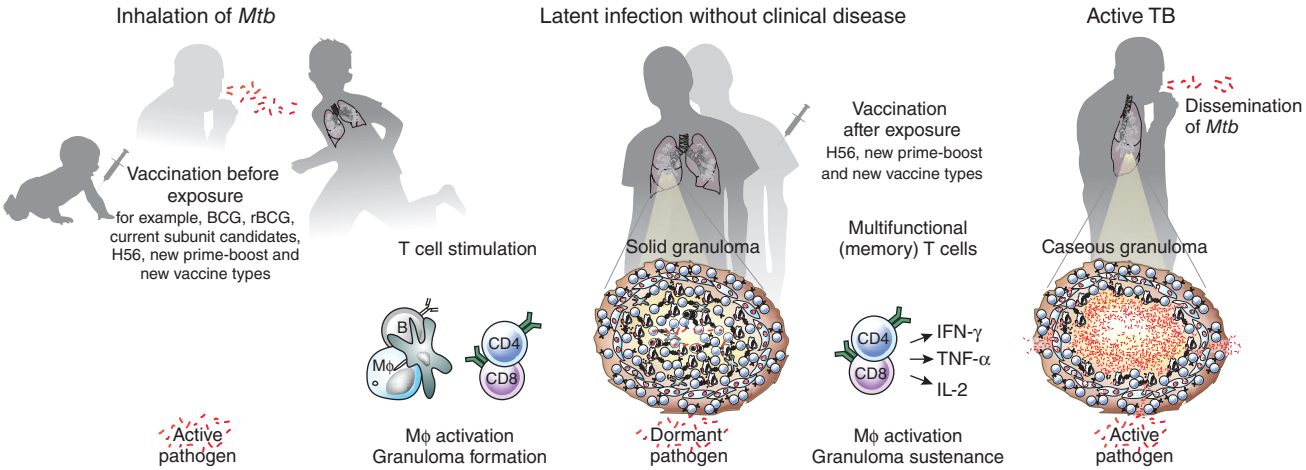

Figure 1 The major steps from infection to disease in tuberculosis (TB) and current and future vaccination strategies against tuberculosis. Infection with the etiologic agent *Mtb* most frequently does not directly result in active tuberculosis. Rather, T lymphocytes induce formation of granulomas, in which *Mtb* is kept under control within macrophages. Polyfunctional T lymphocytes that produce multiple cytokines, including IFN-γ, TNF-α and IL-2, may play a part in the sustenance of solid granulomas and latent infection. During this stage, *Mtb* 'hibernates' in a dormant state. After weakening of the T cell response, active tuberculosis develops. Metabolically active *Mtb* can be disseminated to other individuals. The current BCG vaccine is given immediately after birth and acts as a preexposure vaccine. It protects against severe forms of tuberculosis in childhood. Vaccine candidates currently in clinical trials are also preexposure vaccines that aim to prevent active tuberculosis during an individual's lifetime. H56, the new kid on the block, is active not only before exposure but also after exposure—it can be given to latently infected individuals, of which there are an estimated 2 billion worldwide. Ideally, future vaccines would achieve sterile eradication or prevention of infection with *Mtb*. MΦ, macrophage; DC, dendritic cell; B, B cell; CD4, $CD4^+$ T cell; CD8, $CD8^+$ T cell.

To partly mimic latent infection, Aagaard *et al.*[2] treated *Mtb*-infected mice with antibiotics, which decreased the bacterial load to <100 bacteria per lung. Although *Mtb* regrew immediately after termination of drug treatment, the load remained at approximately 10,000 bacteria over several weeks. Hence, this is not a perfect model of latent infection but may still provide useful insights. Under these latency conditions, post-exposure vaccination of H56 markedly reduced bacterial load, but there was substantial variation in this reduction.

Unexpectedly, in both before- and after-exposure vaccination experiments, compared with the other H56 vaccine antigens, re-stimulation of $CD4^+$ T cells with Rv2660c induced the weakest IFN-γ responses. The antigen seems to have low antigenicity and immunogenicity by itself, but it drives protective immunity when fused to Ag85B-ESAT6. This characteristic might be related to the small molecular weight of Rv2660c.

Vaccination after exposure has been considered risky since 1890, when the first vaccine candidate against tuberculosis did not ameliorate disease in infected individuals and was even harmful[6]. Yet BCG has been repeatedly administered to individuals in several countries[7], and a viral-vector tuberculosis vaccine is safe in latently infected individuals[8]. Perhaps we have to rethink our attitudes toward vaccination after exposure in tuberculosis, and the H56 results provide proof of principle for this type of approach.

The work of Aagaard *et al.*[2] is an important step forward, but the end of tuberculosis vaccine research and development is far from sight. Rather, we have to envisage vaccine development as an iterative process. The first step was the development of numerous preexposure vaccines, but all of these depend on BCG, as they either boost BCG or are genetically modified forms of BCG such as recombinant BCG (rBCG). In newborn individuals who are HIV positive, BCG can cause severe side effects and is therefore not recommended[9], so the next step will be safer vaccines that can be given to these individuals. The H56 vaccine offers such an approach, as it protects independently from BCG.

Next-generation tuberculosis vaccines should aim for sterile eradication or prevention of infection with *Mtb*[10]. The work of Aagaard *et al.*[2] shows that the selection of the right antigens can improve efficacy, and new adjuvants might allow further improvements. Combination vaccinations, for example, composed of rBCG as prime followed by booster with new subunit vaccines, should also be assessed. Rv2660c is present in the BCG genome, but might be insufficiently expressed, as BCG apparently does not become dormant. Hence, rBCG-overexpressing Rv2660c may be needed for optimal prime-boost schedules that include H56. Perhaps the optimal approach would be prevention of infection, which may need totally new types of vaccines, such as those that evoke profound antibody responses in the lung, as this is the major entry point for *Mtb* (**Fig. 1**).

The Stop TB Partnership has announced the goal of eliminating tuberculosis by the year 2050 (ref. 11). With an estimated 8 billion humans worldwide by then, this would mean a reduction from almost 10 million new cases as of today to 8,000 cases in 2050. This ambitious goal can only be achieved through better diagnostics, improved drugs and, most importantly, better vaccines.

COMPETING FINANCIAL INTERESTS
The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturemedicine/.

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