Prospects for new tuberculosis vaccines

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The world urgently requires a new vaccine to combat the problem of tuberculosis (TB). The failure of BCG vaccine, the emergence of extensively drug-resistant TB and the increasing global TB-related mortality has emphasised the urgent need to develop more effective TB vaccines to combat this scourge. The development of new genetic technology and the sequencing of the *Mycobacterium tuberculosis* genome in the late nineties have made the rational development of new TB vaccines a reality.

The ideal TB vaccine should be affordable, especially in the poorest countries of the world where it is most needed, and should be more cost-effective than BCG vaccine. It should be easily administered at or soon after birth, and be safe, immunogenic and effective at all ages and in all populations. It is unlikely that a single new vaccine candidate will meet all or even most of these requirements, and it is likely that more than one new vaccine will be needed.

TB is a leading opportunistic infection in HIV-positive persons. New TB vaccines would therefore have to be safe, immunogenic and effective in this at-risk population as well. Recently the WHO has recommended that children who are known to be HIV positive, even if they are asymptomatic, should not be given BCG vaccine because of the high risk of possibly developing disseminated BCG disease.

TB vaccine strategies

From a public health perspective, delivering a vaccine prior to exposure to mycobacterial infection and preferably soon after birth makes most sense. In high-burden countries this *pre-infection* vaccination strategy will be the ideal option. A second option would be to use a new TB vaccine as a booster some time after neonatal BCG vaccination. A third option is to prevent disease by enhancing or boosting immunity in persons already infected, a *post-infection* vaccine strategy. This approach is attractive because more than 2 billion persons worldwide are already infected and therefore at risk of progression to disease. This is also an attractive option for countries with high rates of HIV, presuming that such a vaccine will be safe in these populations. A fourth option would be to use a vaccine as an adjunct to anti-TB treatment, to shorten therapy or reduce the risk of relapse, a *therapeutic vaccine*. This may be particularly relevant in situations where multidrug-resistant TB cases are common and in areas where TB control programmes are not managing to provide adequate sustainable care.

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New candidate TB vaccines

The last 15 years have seen a number of TB vaccine candidates progressing from concept to laboratory to preclinical studies and finally to clinical trials; more than 200 such candidates have been tested in animals. Currently 4 vaccine candidates are actively being evaluated in human clinical trials. These are MVA85A, Mtb72f, Aeras-402 and *M. vaccae*. There are other candidates, some of which are extremely promising, and these should be entering human clinical trials in the next year or two. All of the candidates developed to date have been shown to be as good as or superior to BCG in animal trials.

MVA85A vaccine (Oxford University, UK)

This subunit recombinant vaccine consists of a specific mycobacterial protein antigen (Ag 85) expressed in a non-replicating viral vector, MVA, a strain of the vaccinia virus. Phase I clinical studies in adults completed in Oxford and The Gambia have demonstrated safety and immunogenicity as measured by *ex vivo* interferon-gamma (IFN-γ) Elispot assay, which assesses specific T-cell responses to tuberculin purified protein derivative (PPD), antigen 85 and its constituent peptides.

A phase II study in healthy, TB-naïve, HIV-uninfected adults and adolescents, half of them BCG-exposed, is ongoing at the South African Tuberculosis Vaccine Initiative (SATVI, see below) site near Cape Town. Preliminary results are promising. Additional South African studies, planned for mid-2007, will test the vaccine's safety and immunogenicity in HIV-infected, TB-infected and HIV-TB co-infected individuals, and then in 168 healthy children and infants.

Mtb72F (Glaxo Smith Klein Biologicals, Rixensart, Belgium)

Mtb72F is a combination of two immunogenic *M. tuberculosis* antigens, Mtb39a and Mtb32a, plus the adjuvants ASO2A or ASO1B.

In 2005, the vaccine entered a phase I clinical trial in healthy TB-uninfected adult volunteers in the USA. It was subsequently evaluated in Belgium in PPD-negative adult

volunteers. In both trials it was found to be immunogenic, safe and well tolerated.

A newer formulation of the vaccine, M72, is currently undergoing clinical trials in Europe, with further trials planned for the SATVI site in South Africa in late 2007.

AERAS-402 (Aeras Global Tuberculosis Vaccine Foundation, Rockville, MD, USA)

This vaccine is intended for use as a boosting vaccine in BCG-primed individuals. The vaccine is a serotype 35 adenovirus which is incapable of replicating and contains DNA that expresses a fusion protein created from three *M. tuberculosis* antigens: 85A, 85B and TB10.4. TB10.4 is a member of the ESAT-6 group of proteins found in *M. tuberculosis* culture supernatants which has been shown to be immunogenic.

This vaccine has undergone phase I studies in the USA and has been shown to be safe. The first trial in South Africa is due to start at the SATVI site near Cape Town in mid-2007.

M. vaccae

M. vaccae is an environmental saprophyte, which is thought to have immunogenic properties which enhance the host immune response. It is has been tested as an adjunct in TB treatment rather than as a preventive vaccine. Its efficacy in preventing TB in HIV-positive persons is also being evaluated in a large Tanzanian clinical trial.

Challenges to TB vaccine development

There are a number of obstacles to overcome in the development of new TB vaccines. These include the lack of a suitable animal model, especially a model mimicking latent or reactivation TB, the absence of a reliable surrogate marker of protection or a correlate of immune protection, the difficulty with field evaluation of TB vaccines, problems with defining clinical endpoints in paediatric practice and lack of resources.

Given the magnitude of the problem worldwide, a global strategy is imperative to co-ordinate collaborative efforts to develop vaccines that are effective in reducing TB. Strategic investments made by the European Union, the National Institutes of Health, the Bill and Melinda Gates Foundation and other agencies and governments have gone a long way towards meeting the intended goal. However, significant additional resources and commitments are needed to support additional research, preclinical development, vaccine production and clinical trials. The Stop TB Working Group on New TB Vaccines has estimated that over $3 000 million will be needed to ensure that we get a new TB vaccine into the field by 2015.

South African TB Vaccine Initiative (SATVI)

The main objectives of the SATVI, a research unit within the Institute of Infectious Diseases and Molecular Medicine at UCT, are to develop the capacity of our rural site in Worcester to do phase I to phase IV TB vaccine trials, to determine important epidemiological characteristics that are of relevance to TB in the area and to identify clinical, microbiological and immunological endpoints of key importance to all stages of vaccine trials. Our immunology studies aim to characterise the human host immune response to TB and BCG vaccination, to identify immune correlates of protection against TB induced by BCG vaccination, and to determine whether BCG vaccination is safe and immunogenic in HIV-infected children. Our flagship project, started in March 2001 and completed at the end of July 2006, showed in a randomised clinical trial equivalence in efficacy between percutaneous and intradermal Japanese BCG in preventing TB in 11 680 infants vaccinated at birth. Nested within this study is a case control study designed to identify correlates of immune protection. We are currently involved in testing a number of new TB vaccines in phase I and II studies.

The work of SATVI is supported by a number of international donors including the Aeras Global TB Vaccine Foundation, the National Institutes for Heath, USA, the European Union and the Welcome Trust.

Conclusion

The current BCG vaccine prevents the invasive complications of childhood TB, such as meningitis and miliary disease, but provides variable protection against adult pulmonary disease. Several new TB vaccines have demonstrated promising results in animal models; a number have gone into phase I clinical trials in humans and have been shown to be safe and immunogenic. It is anticipated that phase III trials will commence by 2009. Licensing of an effective new TB vaccine by 2015 is thus a possibility. The introduction of new TB vaccines is seen as an essential part of the global strategy to eliminate TB by 2050.

Key reading

Ginsberg A. What's new in tuberculosis vaccines. *Bull WHO* 2002; 80: 483-488.

McShane H, Pathan AA, Sander CR, *et al*. Recombinant modified vaccinia virus Ankara expressing antigen 85A boosts BCG-primed and naturally acquired antimycobacterial immunity in humans. *Nat Med* 2004; 10; 1240-1244.

NIH. Tuberculosis Vaccines: State of the Science. http://www.niaid.nih.gov/dmid/tuberculosis/tbvaccine.htm (last accessed 4 April 2007).

Skeiky Y, Sadoff J. Advances in tuberculosis vaccine strategies. *Nature Reviews Microbiology* 2006; 4: 469-476.

Trunz B, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet* 2006; 367: 1173-1180.

World Health Organization. Revised BCG guidelines for infants ar risk for HIV. *Wkly Epidemiol Rec* 2007; 82: 193-196.