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Evaluation of vaccines in the EU TB Vaccine Cluster using a guinea pig aerosol infection model of tuberculosis ☆

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Summary The TB Vaccine Cluster project funded by the EU Fifth Framework programme aims to provide novel vaccines against tuberculosis that are suitable for evaluation in humans. This paper describes the studies of the protective efficacy of vaccines in a guinea pig aerosol-infection model of primary tuberculosis. The objective was to conduct comparative evaluations of vaccines that had previously demonstrated efficacy in other animal models. Groups of 6 guinea pigs were immunized with vaccines provided by the relevant EU Vaccine Cluster partners. Survival over 17 or 26 weeks was used as the principal measure of vaccine efficacy following aerosol challenge with H37Rv. Counts of mycobacteria in lungs and spleens, and histopathological changes in the lungs, were also used to provide evidence of protection.

A total of 24 vaccines were evaluated in 4 experiments each of a different design. A heterologous prime-boost strategy of DNA and MVA, each expressing Ag85A and a fusion protein of ESAT-6 and Ag85B in adjuvant, protected the guinea pigs to the same extent as BCG. Genetically modified BCG vaccines and boosted BCG strategies also protected guinea pigs to the same extent as BCG but not statistically significantly better. A relatively high aerosol-challenge dose and evaluation over a protracted time post-challenge allowed superior protection over BCG to be demonstrated by BCG boosted with MVA and fowl pox vectors expressing Ag85A.

Introduction

Tuberculosis (TB) kills in excess of 2 million people every year and the global epidemic is increasing. The current and only TB vaccine, *Mycobacterium bovis* bacille Calmette–Guérin (BCG), has been applied world-wide for several decades but possesses many drawbacks,[1] including variable efficacy in humans, an inability to protect against re-activation or re-infection, and pathogenicity in the immunocompromised host. Thus, there have been concerted efforts towards the discovery and development of a vaccine to replace BCG. Publication of the complete *M. tuberculosis* genome[2] and developments in both laboratory and 'in silico' methods of screening large numbers of proteins for immunogenicity has now accelerated the process of antigen discovery. In addition to the growing number of potential antigens, novel adjuvants and delivery systems are continually being developed.

The TB Vaccine Cluster project funded by the European Union Fifth Framework programme aimed to develop novel vaccines against tuberculosis that would be superior to BCG and suitable for evaluation in humans. This included a step-wise evaluation of new candidate vaccines in mice, guinea pigs and non-human primates. Mouse studies enabled the initial selection of promising candidates by measuring the immunogenicity and protection against virulent challenge, and these candidates were then evaluated using the more discriminative aerosol-infection guinea pig model. Criteria for the selection of candidates for evaluation in the guinea pig model included evidence of immunogenicity and protective efficacy equivalent to or better than BCG in mouse and in some cases guinea pig models. The programme provided an opportunity to directly compare, within a single experiment, a number of vaccine candidates which had previously been demonstrated to be efficacious when evaluated separately. Here, we report the results of these comparative studies.

Materials and methods

Vaccines

The vaccines evaluated in the studies are listed in Table 1. The source of each vaccine is given and,