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Use of recombinant virus-vectored tuberculosis vaccines for respiratory mucosal immunization

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Summary Recombinant virus-vectored TB vaccines represent the most promising vaccine platform for boosting the protective immunity mediated by parenteral BCG prime immunization. A major advantage associated with virus-vectored vaccines is that they are potent respiratory mucosa-deliverable vaccines. A recombinant replication-deficient adenoviral (Ad) vector was engineered to express *Mycobacterium tuberculosis* (*M.tb*) Ag85A. Single administration of this Ad vaccine via the intranasal, but not intramuscular, route provided potent immune protection from pulmonary *M.tb* challenge. Respiratory mucosal boosting immunization with Ad vaccine was effective in enhancing T-cell activation and immune protection following parenteral DNA or BCG prime immunization. We have also recently developed a recombinant vesicular stomatitis virus-vectored (VSV) TB vaccine. Ad and VSV vector systems will be complementary to each other for BCG prime—virus vaccine boost immunization protocols.

Introduction

Pulmonary tuberculosis (TB) is one of the leading causes of deaths by a single infectious agent. Two million people die of TB and 8.3 million develop TB every year worldwide. One-third of the world population has been infected by *Mycobacterium tuberculosis* (*M.tb*) (latent TB) and about 5–10% of these people will develop TB disease sometime in their lives (re-activation).[1] The current licensed vaccine against TB, bacillus Calmette–Guérin (BCG), has been used globally for 80 years with demonstrated efficacy in protecting from childhood TB. However, BCG has failed to control adult TB, perhaps primarily due to the fact that BCG is given once or twice shortly after birth in most countries and BCG-mediated protective immunity wanes in 10–15 years.[2,3] Undoubtedly, there is a need to develop ways to improve the efficacy of TB vaccination. Over the last couple of decades, an

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enormous effort has centered on developing new vaccine formulations that may be more effective than BCG with the hope that some of these candidate vaccines may have the potential to replace BCG as a primary TB vaccine.[4,5] However, not only have the majority of novel TB vaccine formulations failed to be superior to the current BCG in experimental models, it is increasingly realized that more effort needs to be made for developing effective boosting vaccines for BCG vaccines including those who have been latently infected with *M.tb* (post-exposure vaccines).[6] This conviction is based on several considerations: (1) it is unlikely that a single use of any vaccine will be able to generate long-lasting quality anti-TB memory T cells; (2) BCG and the associated infrastructure have been used for 85 years with 85% of people being BCG-vaccinated; BCG vaccine is effective in controlling childhood TB; (3) ethically it will not be allowed to include a control group that does not receive BCG in a field trial for evaluation of new TB vaccines in TB-endemic countries (different from AIDS/malaria for which there is no licensed vaccine); this fact impedes the ultimate definition of a vaccine that may have a potential to replace the current BCG as a primary TB vaccine; (4) both clinical and experimental evidence indicates that BCG is an ineffective boost vaccine in BCG vaccines. Furthermore, while there is no doubt of the importance of academic TB vaccine research, there is always a need to consider the practical issues related to any given vaccination program in terms of the simplicity of vaccine formulation, and the cost and the vaccine stability. In addition, it is also important to consider that TB is primarily a respiratory mucosal infectious disease and a mounting body of evidence indicates that mucosal vaccination provides the best protection against mucosal infectious diseases whereas BCG has been given to humans per-cutaneously. In this regard, the majority of new vaccines currently under development are either ineffective or unsuitable for respiratory mucosal vaccination.[5,7]

There are 4 major types of TB vaccines under development: mycobacterial organism-based, protein-based, plasmid DNA-based and viral-based. Replication-competent mycobacterial organism vaccines are unable to effectively boost BCG-triggered immune responses (homologous prime-boost regimen).[8,9] Furthermore, although live organism-based vaccines can be effective respiratory mucosal vaccines, they are considered unsafe for respiratory mucosal application in humans since they will cause undesired chronic immunopathology in the lung. On the other hand, while both protein- and DNA-based TB vaccines, upon parenteral administration as a boost vaccine, have demonstrated varying boosting effects on BCG-triggered immune activation, they are generally ineffective mucosal vaccines with very few exceptions.[10–13]

Hence, in comparison, recombinant viral-vectored TB vaccines have the advantage of being safe and effective for respiratory mucosal administration and suitable for effective heterologous boosting of BCG-primed individuals.[14] To date, both the modified vaccinia virus Ankara (MVA) and adenovirus (Ad) have been well explored for their applications as TB vaccines.[14,15] The results from a phase I clinical evaluation of MVAAg85A have recently been published.[16] The other viral TB vaccines that have been developed, or still under development, include fowlpox[17] and influenza viruses (Dr. Andrej Egorov-Cuba 2005 International TB Vaccine Workshop presentation). In addition to recombinant Ad-vectored TB vaccines, we have also been developing recombinant vesicular stomatitis virus-vectored TB vaccines. We believe that these virus-vectored TB vaccines represent potent boost vaccine platforms for BCG prime immunization and in the years to come, we will be able to come to a better definition of their relative potency and suitability for future human applications.

Adenoviral vector system

Ads are double-stranded DNA viruses with a 36 kb genome. Ad has an excellent safety record for human use since a live wild-type Ad has been given to about 10 million army recruits in North America.[18] Recombinant Ads were initially exploited as gene replacement vectors for gene therapy.[19,20] However, this approach has proven ineffective due to the transient nature of transgene expression and the potent immunogenicity of Ad backbone. Ad was later used as a gene transfer vector for in vivo functional studies of specific proteins, such as cytokines.[21,22] In this regard, Ad vectors are beneficial due to the high levels of transgene expression compared to other gene transfer systems. Indeed, to date, Ad vectors have remained one of the most popular gene transfer vectors used in gene-based clinical trial protocols (about 1/3), mostly for angiogenic applications and cancer immunotherapeutic studies.[20] More recently, Ad vectors have been used as a vaccine vector against infectious diseases and several Ad-vectored vaccines have progressed into non-human primate studies and clinical trials.[7,23] An Ad5 vaccine expressing the Human Immunodeficiency Virus (HIV) gag gene induces gag-specific CD8 T-cell responses in healthy human subjects in phase I clinical studies.[24] Currently, phase I trials are being carried out and