CHAPTER I

Introduction

*M.tuberculosis, the captain of the men of death.*

...Sir William Osler
In the future the fight against this terrible plague of mankind will deal no longer with an undetermined something, but with a tangible parasite, whose living conditions are for the most part known and can be investigated further.”

*...Robert Koch, 1905*

More than 2000 years ago in ancient Greece, Hippocrates described a common illness that he called “phthisis”. This was the same disease that we today call tuberculosis (TB). At the dawn of the new millennium, we are still mute witnesses to the silent yet efficient march of this sagacious disease, its myriad manifestations and above all its unequalled vicious killing power. It is the only infectious disease declared by World Health Organization (WHO) as a global health emergency in 1993. *Mycobacterium tuberculosis*, the etiological agent of TB, is one of the most effective human pathogens that is responsible for 1.4 million human deaths and 8.7 million new TB cases each year globally (1 death every 20 seconds) (WHO, 2012). Tuberculosis is a global health problem of monumental proportions. Approximately, 2 billion people worldwide are asymptomatically infected with *M.tuberculosis* and constitute a major impediment to global public health control measures.

The development and widespread administration of *M.bovis* BCG vaccine since the early 1920s was originally hailed as a major breakthrough with the promise of eradication of the scourge of TB from the world (Aronson, 1948; Aronson *et al.*, 1958; Hart, 1967; Hart and Sutherland, 1977; Trial, 1980; Colditz *et al.*, 1994; Aldwell *et al.*, 1995; Brosch *et al.*, 2007; Walker *et al.*, 2010; McShane, 2011). However, the early promise was not realized and with the growing incidence of TB cases and inconsistent protective efficacy of BCG, it became evident that the BCG vaccine, in its existing form, is of limited use in controlling the disease particularly in the elderly (Fine, 1995). Therefore, the need to develop a superior TB vaccine than BCG cannot be overemphasized. The purpose of an effective live vaccine would be best served if the vaccine strain is antigenically as similar as possible to the disease-causing pathogen in order for it to generate the host immune responses that mimic natural infection (Brodin *et al.*, 2004). Comparative genomic studies have revealed that BCG, in comparison to *M.tuberculosis*, lacks 16 defined regions (RD1-16) comprising of ~150 genes, some of which are known to encode potential antigenic determinants that could significantly contribute to the immunogenicity of a vaccine (Behr *et al.*, 1999; Brosch *et al.*, 2007). This makes the use of
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attenuated *M.tuberculosis* strains rather than BCG, for the generation of appropriate immune responses, an attractive idea (Sambandamurthy and Jacobs, 2005; Hernandez Pando *et al.*, 2006; McShane, 2011). Moreover, the availability of complete *M.tuberculosis* genome sequence and an increased understanding of the genes involved in *M.tuberculosis* virulence has led to a renewed optimism that it should be possible to develop more efficient TB vaccines than the existing BCG (Cole *et al.*, 1998; Camacho *et al.*, 1999).

Most of the TB cases can be cured with the existing drugs isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA) in a 6-9 months regimen. TB treatment strategy begins with reiteration that quality DOTS and proper implementation of its essential elements are the *sine-qua-non* for TB control. However, the existing chemotherapy has two caveats namely, long treatment duration and inability to impart sterilizing immunity (Riccardi *et al.*, 2009). Non-compliance to such a prolonged regimen often leads to the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB along with the increased incidence of disease reactivation (Chiang *et al.*, 2010; Marahatta, 2010). Moreover, incomplete treatment often leads to increased transmission of the disease. Even if a patient successfully completes the chemotherapy, the current therapy is unable to impart complete sterilization, hence, there is a 5-10% lifetime risk of reactivation of the latent infection (Narayanan *et al.*, 2010; WHO, 2012; Satti *et al.*, 2013). This risk substantially increases to 10% annual risk in the immuno-compromised individuals (Manabe and Bishai, 2000). Hence, alternate strategies are urgently required that can shorten the duration of chemotherapy and reduce reactivation of the disease.

In this study, we have attempted to evaluate both the prophylactic as well as immunotherapeutic strategies for vaccination against tuberculosis. Firstly, by deleting the function of three virulence associated genes of *M.tuberculosis*, namely, *mptpA* (Rv2234) and *mptpB* (Rv0153c) (both encoding secretory tyrosine phosphatases) and *sapM* (Rv3310) (encoding another secretory acid phosphatase), we have developed the mutant MtbΔmms and have evaluated its protective efficacy in the guinea pig model of experimental tuberculosis. Secondly, we have evaluated the immunotherapeutic potential of adjunctive immunotherapy with DNAacr (DNA vaccine expressing *α-crystallin* gene of *M.tuberculosis*) and DNAsod (DNA vaccine expressing *superoxide dismutase* gene of *M.tuberculosis*) in a murine model of latent TB to shorten the duration of chemotherapy and to prevent the reactivation of latent infection.
REFERENCES


