CHAPTER 1
INTRODUCTION
Tuberculosis remains a major health problem worldwide, with seven million new cases appearing every year, accounting for 4 million deaths per year (Holm, 1984; Warren, 1985). It is still a great killer in developing countries with a mortality rate of 60 to 100 per hundred thousand as compared to one to two in industrially developed nations (Park and Park, 1984). The chronic nature of the disease, the ability of the tubercle bacilli to remain alive in the human body for several years and the emergence of drug resistant strains demands a good and effective vaccine (Zaki, 1971).

BCG, the Bacille Calmette Guerin, has been the vaccine widely used to confer immunoprophylaxis against this disease. It has, however, given a protection varying from nil to 80% in different parts of the world (ten Dam et al., 1976). It was found effective in United Kingdom, while in Puerto Rico, Georgia and Alabama, it conferred a low level of protection (Sutherland, 1971a). A long-term well controlled efficacy study conducted in South India by the Indian Council of Medical Research (ICMR) in collaboration with World Health Organisation (WHO), showed no protection by BCG against pulmonary tuberculosis in the subjects in the first seven and half years. However, after twelve and half years, a maximum protection of 20 - 28% was observed (Tripathy, 1983; 1986). The variable level of protection conferred by BCG is ascribed mainly to two factors: the modulating influence of environmental mycobacteria on immune response (Stanford and
Rook, 1983) as also the genetic predisposition. The importance of genetic background of the host in the immune response to BCG is indicated by experimental studies conducted in different inbred strains of mice (Forget et al., 1981; Skamene et al., 1982). In mice, the early host response to i.v. infection with small doses of dispersed \textit{M. bovis} BCG (Strain Montreal) as well as a variety of BCG sub strains is controlled by the Bcg gene. BCG-resistant (Bcg$^r$) mice prevent net growth of \textit{M. bovis} BCG in their reticuloendothelial tissues, whereas there is a progressive multiplication of mycobacteria in the organs of BCG-susceptible (Bcg$^s$) mice (Forget et al. 1981; Gros et al., 1981). Since the bacillary load which develops in mice infected with low doses of \textit{M. bovis} BCG is controlled by Bcg gene, this locus has influence on the quality and quantity of immune response developed on secondary challenge. \textit{M. bovis} BCG confers immunity to the BCG-susceptible strains (BALB/c By J, C57BL/6 N Cr1 and B10 A, Bcg$^s$) and not to BCG-resistant strains (CBA/N, C3H/He Ncr1 and A/J, Bcg$^r$) against a secondary infection with homologous and heterologous pathogens (Pelletier et al., 1982). Genetic predisposition may probably explain the variable efficacy of BCG observed in different human populations. Hence, a case exists for an alternate and more effective vaccine conferring better immunity against tuberculosis in heterogeneous populations.

In recent years, two candidate vaccines (ICRC-PP1 and \textit{M. w}) have been evolved for leprosy in India based on the
screening of a large number of mycobacteria for their ability to induce desirable cell mediated immunity. (Talwar, 1978b; Deo et al., 1981). One of these is an atypical, cultivable non-pathogenic mycobacterium, Mycobacterium w. This bacillus is a fast grower and resembles in its metabolic properties to the mycobacteria in Runyon Group IV. This bacillus in killed form has been found to be highly effective in upgrading the immunity in leprosy (Talwar, 1978a). M.w vaccine is approved for human use and is currently in Phase II/III immunotherapeutic and immunoprophylactic trials in multibacillary leprosy patients where it has expedited clinical improvement, accelerated bacterial clearance and upgraded immunological responses to M.leprae antigens. Initial results of the trial have been communicated (Talwar et al., 1989; 1990a; 1990b). M.w shares T cell antigens (Mustafa, 1988) and B cell antigens (Ganju et al., 1990) with M.leprae and M.tuberculosis.

The present study was undertaken to assess the potential of M.w for conferring protection against M.tuberculosis, keeping in view the following aims and objectives:

1. To study the protective efficacy of M.w in inbred strains of mice that are non-responders to BCG (Bcg\textsuperscript{r}).

2. To determine whether M.w can or cannot immunize both the BCG responder (Bcg\textsuperscript{s}) and BCG non-responder (Bcg\textsuperscript{r}) genetic strains of mice.
3. To investigate the immunizing potential of M. w in guinea pigs for protection against tuberculosis.

4. To carry out studies on the possible mechanism by which protection is attained.