1. INTRODUCTION

One third (~32%) of the world population is infected with tuberculosis (TB), a chronic contagious disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), which spreads through aerial route via. aerosol and droplet nuclei from sneezing and coughing of infected patients. TB is commonly a pulmonary disease but also affects other organs like bones, the central nervous system (CNS), lymph nodes, pleura, genitourinary tract, bones etc. Tuberculosis of organs other than lungs i.e. extra-pulmonary tuberculosis (EPTB) accounts for 10-15 % of total cases of tuberculosis in India (Sharma and Mohan 2004), and continues to be a major cause of illness, disability, and premature death throughout the world.

In 1997, the World Health Organization (WHO) carried out the first worldwide survey of the global burden of tuberculosis and estimated that on average, one person is infected with tuberculosis every second of each day. In fact, *M. tuberculosis* is the single largest killer being responsible for 26% of avoidable adult deaths worldwide (Dye *et al.* 1999). Globally 8.6 million new cases were accounted in the year 2012. India being a densely populated country has the highest TB burden accounting for one fourth of the global incidence and 2/3rd of the cases in south East Asia. Currently 2.3 million new cases of TB occur in the country annually, of which about 1.3 million are infectious new smear positive pulmonary TB cases. Further, India also has a high-burden of drug-resistant TB cases (WHO 2013). The phenomenon of drug resistance in TB was observed as early as 50 years ago. The Multi Drug Resistant Tuberculosis (MDRTB) term is used for tuberculosis resistant to at least Rifampicin (RIF) & Isoniazid (INH) (Espinal *et al.* 2001). The widespread development and subsequent transmission of MDR-TB in regions suffering from collapsing public health infrastructure has added yet another dimension to the difficulties in controlling this ancient human disease (Katoch 2010).
Tuberculosis related prevention and control activities appear even more challenging owing to the presence of a wide range of socioeconomic variations, health care delivery system related factors, poor ventilation, slum population, overcrowding and low level of awareness among the general population. In India, traditional private practitioners practicing traditional and alternative medicine run successful practices as they are cheap, available in any rural or urban area are culturally acceptable and are often extremely popular. Most of households consult the private sector for treatment of minor and major illnesses including tuberculosis.

The epidemiology of tuberculosis has changed dramatically over the last decade in some parts of the world; human immunodeficiency virus (HIV) infection has struck a detrimental blow to even well-functioning TB control programs. The impact is so massive that, despite improvements in case-finding and treatment completion, tuberculosis increased at an annual rate of 1% worldwide (Deivanayagam et al. 2002). Risk of development of active TB in HIV infected cases is 20 times higher than non-HIV patients and it accounts for one-third of the Acquired Immuno Deficiency Syndrome (AIDS) death worldwide.

The aim of present day chemotherapy includes the rapid killing of active bacilli and clearing dormant bacilli thus, reducing the risk of drug resistance and relapses. It involves the use of various first line drugs like Rifampicin, Isoniazid, Pyrazinamide, Ethambutol and Streptomycin. In the year 1992 Govt. of India WHO and World bank together reviewed national tuberculosis programme (NTP) and revised national programme (RNTCP) was incepted in 1997 (Park, 2013a). The success rate of RNTCP has been 85% among new smear positive cases since it covered the whole country March 2006 (RNTCP and others 2008). Resistance to isoniazid (INH) is the most common form of mono resistance with a prevalence of 10% among new tuberculosis (TB) cases and 28% among retreatment cases reported in 2009 globally (WHO 2008). WHO currently recommends for INH resistant TB patients, a daily regimen of Rifampicin, Pyrazinamide and Ethambutol for a period of 6-9 months with
added fluoroquinolones among those with extensive disease (WHO 2009). However, the RNTCP in India continues to use the standard eight-month retreatment regimen, administered thrice-weekly (2H3R3Z3E3S3/1H3R3Z3E3/5H3R3E3; H-Isoniazid; R-Rifampicin; Z-Pyrazinamide; E-Ethambutol; S-Streptomycin) for TB patients with INH resistance (Park, 2013b). Thus understanding and checking INH resistance is most important to combat drug resistant TB.

The present thesis is aimed to investigate the factors regarding the Isoniazid pharmacogenomics and to understand in-depth information about cumulative mechanisms underlying patient therapeutic responses. Impaired INH metabolism is associated with polymorphisms within the NAT2 gene (Kita et al. 2001) and it is therefore possible that a fast acetylator genotype (Parkin et al. 1997) can indirectly contribute to the INH resistant phenotype in *M.tuberculosis* by lowering the serum concentration of the drug. Slow acetylators are able to inhibit a significant proportion of the INH resistant mutants, whereas the serum concentrations of fast acetylators cannot do this (Gangadharam et al. 1961). It is hypothesized that a fast acetylator genotype may indirectly contribute to mycobacterial adaptation to INH, since the time of bacterial exposure to INH is limited and thus small systemic concentrations might lead to the gradual build-up of INH-resistance.