Introduction
Microbial pathogens employ a variety of strategies to establish infection in a susceptible host. Pathogenic *Salmonella* species, which cause a number of clinical manifestations in animals and humans, produce a large array of effectors which they use to penetrate intestinal mucosa, bring about cellular cytotoxicity, ensure their intracellular replication and promote systemic dissemination (Patel *et al.*, 2005; Ohl and Miller, 2001; Jones and Falkow, 1996). In spite of functional conservation of these effectors amongst various *Salmonella* serovars, many of them exhibit a high degree of host species specificity. *Salmonella typhi*, ingested through contaminated food or water, causes a generalized systemic infection, typhoid, exclusively in humans and higher primates (chimpanzees). On the other hand *Salmonella typhimurium*, which shares more than 90% genomic information with *S.typhi*, causes only localized self-limiting gastroenteritis in humans (Benjamin *et al.*, 1990; Plant and Glynn, 1979). The reasons for this difference in clinical manifestations brought about by these two closely related *Salmonella* species are poorly understood. Unlike *S.typhi*, infection of humans with *S.typhimurium* is believed to be associated with a potent inflammatory response in the gut, which might contribute to faster clearance of the pathogen. *S.typhi* either lacks molecules that can trigger such inflammatory responses in the gut, or has devised ways to modulate such kind of host responses.

In mice, *S.typhi* and *S.typhimurium* behave differently. While the former does not cause any pathogenesis, the latter produces a systemic infection that is analogous to human typhoid. Most of our current understanding of host-pathogen interactions during infection with pathogenic *Salmonella* is largely based on studies carried out in *S.typhimurium* mouse model (Hensel *et al.*, 1995; Gulig and Curtiss, 1988; O'Brien, 1982). These studies have shown that both innate and adaptive immune responses are essential for protection against pathogenic *Salmonella*. Innate immunity is primarily produced through activation of
pathogen sensors, including Toll-like receptors (TLRs), and intracellular sensors, like Nods (Delbridge and O'Riordan, 2007; Meylan et al., 2006). Mice deficient in, for example, TLR-4 that recognizes bacterial lipopolysaccharide (LPS), are more susceptible to *S. typhimurium* infection, highlighting the importance of this receptor in host defence against this pathogen (Vazquez-Torres et al., 2004). While innate immune responses are vital for immunity during early stages of infection, eventual clearance of the pathogen and long-term immunity is dependent on cell-mediated immunity (CMI). The quality and magnitude of CMI is, however, regulated to a large extent by innate immune responses. The significance of adaptive immunity during infection with *Salmonella* has been revealed by adoptive transfer experiments and by studies carried out in mice deficient in T cells. It has been demonstrated that both CD4+ and CD8+ T cells are important for an effective immune response to *Salmonella* (Mastroeni et al., 1993a; Nauciel, 1990). It has also been established that T_H1 type of T cells that secrete IFN-γ are vital to clearance of *Salmonella* infection (Pie et al., 1997). IFN-γ activates macrophages, the main cell type in which *Salmonella* resides during systemic infection (Richter-Dahlfors et al., 1997). Mice deficient in IFN-γ receptor are unable to resolve *Salmonella* infection (Lalmanach and Lantier, 1999) further reiterating the role of IFN-γ in protective immunity against this pathogen. All these studies suggest that clearance of *Salmonella* from the system and long-term immunity against infection with this pathogen is dependent on efficient activation of T cells. Pathogenic *Salmonella* species must therefore devise strategies to manipulate the immune system in a manner that deregulates activation of this arm of immunity. Many studies have reported that pathogenic *Salmonella* can modulate functions of macrophages and dendritic cells (Galdiero et al., 2003; Li and Cherayil, 2003; van der Velden et al., 2003; Dragunsky et al., 1990). There is also evidence to suggest that *S. typhimurium* might suppress murine T
cell functions *in vitro* (Gupta, 1998). However, considering that *S. typhi* and *S. typhimurium* produce different manifestations in humans, it is not certain whether host-pathogen interactions found important from the mouse model would be relevant to the interactions of *S. typhi* with human cells. In fact, many recent studies suggest that conclusions about *S. typhi* pathogenesis drawn from the mouse model need to be revised (Nguyen *et al.*, 2004; Pier *et al.*, 1998; Weinstein *et al.*, 1997; Pascopella *et al.*, 1995). There have been no detailed studies on the interaction of *S. typhi* with cells of the immune system, in particular with T cells, which as discussed above, forms a vital component of immunity against pathogenic *Salmonella*. One major stumbling block to carry out such studies has of course been the lack of animal model for *S. typhi*. A study carried out by Rajagopalan *et al.* in 1982 with peripheral blood cells from typhoid patients suggested that infection with *S. typhi* might lead to increased numbers of T suppressor cells (Rajagopalan *et al.*, 1982b). However, other than this study, which did not carry out any functional characterization of the suppressor T cells, there is very little information available about how *S. typhi* might be countering the immune system in order to establish infection in humans. This forms the rationale of the present study, which was designed to investigate the possible role of bacteria associated and/or bacteria-released molecule(s) from *S. typhi* in the modulation of T cell activation.