INTRODUCTION

Helminth infections

Helminth parasites are complex eukaryotic organisms, characterized by their ability to maintain longstanding infections in humans, sometimes lasting decades. Hence, parasitic helminths are a major health care problem worldwide, infecting approximately 2 billion people in the tropics and subtropics, mostly in resource-limited countries. The three most commonly prevalent helminth infections are the hookworm infection, lymphatic filariasis and strongyloides infection. Although these helminths fall under the broader category of parasites, these helminths’ mode of infection and its site of infection is different. Hookworm infections are common intestinal helminth infections (affecting 740 million people worldwide) known to cause intestinal injury and blood loss (Hotez et al., 2004). Lymphatic filariasis is caused by Wuchereria bancrofti and strongyloidiasis is caused by Strongyloides stercoralis together infecting close to 250 million people worldwide (Babu and Nutman, 2013), (Bonne-Annee et al., 2011). Both hookworm and strongyloides infection are transmitted by contaminated soil coming in contact with the host’s skin and the site of infection is in the intestine, whereas filariasis is transmitted by blood meal of infected mosquitoes and the site of infection is systemic. In addition, these helminth infections are often clinically asymptomatic due, in large part, to the parasites’ ability to manipulate the host immune system, a feature that insures their survival largely because of their ability to restrict local inflammatory pathology (Maizels and Yazdanbakhsh, 2003), (Allen and Maizels, 2011). Generally helminth infections induce strong Th2 immune responses in the host which is represented by the classic Th2 cytokines like IL-4, IL-5,
IL10 and IL-13. These cytokines help in controlling tissue damage by mucus secretion, goblet cell hyperplasia and eosinophil influx.

**Tuberculosis**

*Mycobacterium tuberculosis* (*Mtb*) infects approximately 2 billion people worldwide, with 90% of *Mtb*-infected individuals having latent infection. The control of *M. tuberculosis* infection requires a clearly delineated Th1 response (IL-12, IFN-γ, and TNF-α) and, to a lesser extent, a Th17 response (IL-17 and IL-23). Both Th1 and Th17 responses have been shown to be important in the induction and maintenance of protective immune responses in mouse models of *Mtb* infection or for control of human *Mtb* infection (as seen in latent tuberculosis [LTB]) (Ernst, 2012), [Walzl et al., 2011]. During latency, *Mtb* is contained within granulomas, where the mycobacteria reside in macrophages and in which growth and replication appear to be constrained. Maintenance of the granulomatous lesion is mediated by CD4+ and CD8+ T cells (Ulrichs and Kaufmann, 2006). *Mtb* induces prototypical Th1 and Th17 responses in CD4+ and CD8+ T cells both in mouse models and in human infection. Multifunctional CD4+ Th1 cells, co-expressing IFN-γ, TNF-α, and IL-2 and dual-functional cells expressing IFN-γ/IL-2 and IFN-γ/TNF-α have been shown to be associated with protection against active pulmonary disease in tuberculosis (TB) (Millington et al., 2007), (Day CL et al., 2011), (Harari A et al., 2011).

**Helminths and Tuberculosis**

Helminth infections occur throughout the tropics and subtropics and in many regions of the world and have an overlapping geographic distribution with *Mtb*. In terms of interaction in human TB, filarial infections have been shown to alter the antigen-specific protective immune responses in latent TB by modulating the Th1 and Th17 responses to
Helminth infections are strongly associated with an IL-10 dominant regulatory environment that could potentially down modulate antigen-specific responses to third party antigens (Metenou et al., 2012). Multifunctional CD4$^+$ Th1 cells and to a lesser extent Th17 cells have also been shown to play a role in protection against TB, however, the role of multifunctional Th17 cells, if any, in active human pulmonary TB remains unexplored. Type 1 and Type 17 cytokine production by CD8$^+$ T cells is also thought to play an important role in protection against TB infection/disease (Cooper, 2009). Finally, both filarial parasites (present in the circulation) and hookworm and Strongyloides (which is an intestinal helminth but has a lung migratory larval stage) could directly influence the outcome of TB infection. We therefore hypothesized that immune responses in both latent and active TB might be modulated by the regulatory immune networks often seen in chronic helminth infections that could have a negatively impact on the course of active tuberculosis.