Summary and Future Prospective

The main theme of the thesis was to understand the role of host xenobiotic nuclear receptors which plays a crucial role in host drug metabolism in different pathophysiological conditions such as infection, inflammation and cancer.

Infectious diseases are pathological condition caused by microorganisms such as bacteria, viruses, fungi, or parasites and are the leading cause of mortality worldwide, particularly in low income countries. In our study we used TB as a model of infectious disease because it is a leading cause of death due to a single infectious agent in low income countries including India. Despite significant efforts in TB disease research and treatment, the control and eradication of diseases faces major challenges. TB is mainly caused by intracellular bacteria *M. tuberculosis* and the multidrug chemotherapy for tuberculosis is proved successful against *M. tuberculosis* and has yielded immense public health benefits. The current challenge in TB treatment is the rapid increase in the emergence of drug resistant TB and this necessitates finding new drug targets, new drug molecules and alternative therapeutic strategies that can be effective against the resistant TB bacteria and are less likely to induce drug resistance. The emphasis has also been to develop host directed therapies that swing host cellular defense strategies against *M. tuberculosis*. Host directed therapies impairs *M. tuberculosis* survival and replication either by disrupting the host signaling pathways used by the bacilli during infection or by augmenting the host immune response to *M. tuberculosis*. In this study we addressed the role of Xenobiotic nuclear receptors (PXR and CAR) in intracellular survival and TB drug non-responsiveness of *M. tuberculosis*. We performed loss of function experiments by silencing these xenosensors and concluded that PXR and CAR augments *M. tuberculosis* survival and contributes to drug non-responsiveness to front line TB drug isoniazid. Furthermore, we also explored the detail mechanisms by which human PXR modulates *M. tuberculosis* survival and drug non-responsiveness in hMDMs. PXR augments *M. tuberculosis* survival inside the macrophages by dampening host defense mechanisms (such as phagolysosomal fusion, pro-inflammatory cytokine production, and apoptosis) and also induces drug non-responsiveness to frontline TB drug rifampicin. In addition, *M. tuberculosis* cell wall lipids, also modulates PXR activity by interacting with its promiscuous ligand-binding domain. Therefore targeting PXR in *M.*

tuberculosis infection can prevaricate phenotypic drug non-responsiveness to TB drugs and could be a promising adjunct therapy.

Inflammation acts as a double-edged sword; it provide protection from invading pathogens, however, on the other hand an uncontrolled chronic inflammation due to inappropriate activation of inflammatory lymphocytes may lead to damage of self-tissues and organs which is a key component in autoimmune, metabolic and neurodegenerative disorders. $CD4^+$ Th1 and Th17 cells play a crucial role in many autoimmune diseases. Therefore, it is important to investigate how to control these cell types to prevent the progression of these inflammatory diseases. In chapter 4 we showed that xenobiotic nuclear receptor PXR activation by small molecule activator PCN decreases the severity of autoimmune disease progression in mouse model of autoimmune disease and down regulates the expression of IFNγ and IL17A, the hallmark cytokines of Th1 and Th17 cells respectively. In addition the expression of PXR was found to be down regulated in cells isolated from inflamed tissues. These observations collectively suggest that PXR exhibits an anti-inflammatory role in mice model of autoimmune disease. In future, we need to identify the molecular mechanisms by which PXR down regulates the expression of IFNγ and IL17A in $CD4^+$ Th cells.

In chapter 5, we have pursued the role of TGF-β in cancer drug resistance. Recent studies highlight the role of TGF-β in development of chemotherapeutic resistance in various cancers. But the mechanisms by which it induces drug resistance in not clear. In this study we demonstrated the mechanisms by which TGF-β induces drug resistance in HepG2 cells. TGF-β sensitized HepG2 cells exhibit resistance to standard anti-cancer drugs such as docitaxol and doxorubicin by modulating xenobiotic nuclear receptor PXR and its target genes. To support our *in vitro* observations, further studies using *in vivo* models would be compelling.