SUMMARY AND FUTURE PROSPECTIVE

This thesis describes the function of an endocrine NR 'VDR' and an orphan NR 'TR4' in infection and inflammation. We have also made an attempt to understand the small molecule-NR interactions and in the course of time we generated small molecule databases for orphan NRs and autophagy modulators.

Uncontrolled inflammation may result in damage to self-tissues and organs, due to inappropriate activation of inflammatory lymphocytes. Th1 and Th17 are the two Th cell subsets that induce several autoimmune diseases. So it is important to investigate how we can control these cell types to prevent the progression of these inflammatory diseases. In chapter 3.1, we showed that VDR directly binds to the promoter of and inhibits Smad7 expression, which is a negative regulator of TGFβ-Smad pathway. Further VDR also activates ERK in Th17 cells, thereby inhibiting Th17 cells and creates a milieu for the expression of anti-inflammatory TFs Foxp3 in Th17. In this chapter, we have also validated our *in-vitro* findings in an *in-vivo* EAE mice model. In chapter 3.2, for the first time we have identified the role of TR4 in Th17 cells. We showed that TR4 can directly bind to the promoters of Th17 master TF *RORγt* and *IL23R*, thereby suppressing their expression. This story further confirms and ascribe an anti-inflammatory role of TR4 by inhibiting Th17 cell differentiation. In future, we need to identify co-repressor partner of TR4 on *rorγt* and *il23r* promoters, and we also need to extend further our *in-vitro* finding to an *in-vivo* EAE animal model.

M. tuberculosis is an infectious intracellular pathogen, the causative organism of TB, and its one of the leading cause of death in the world. TB is the one of the global health issue because of the remarkable ability of these bacteria to avoid host defense mechanism to survive and also because of the development of drug-resistant variants of this organism. Hence, there is an urgent need for the design of novel strategies to fight against this pathogen. Our approach should be to understand host factors that are crucial for the killing of the bug. It will be novel to exploit host factors that modulate the clearance or survival of the pathogen in the host while targeting pathogen with frontline drugs. In chapter 4.1, we have identified the role of protein tyrosine phosphatase SHP1 in $1,25(OH)_2D_3$-VDR induced autophagy. We showed that SHP1 inhibitor SSG inhibited $1,25(OH)_2D_3$ induced autophagy. We also proved that $1,25(OH)_2D_3$-VDR induces SHP1

expression by directly binding to its promoter. This story identified novel $1,25(OH)_2D_3$-VDR-SHP1-PI3K-AKT pathway of autophagy modulation. We need to study further the role of identified signaling pathway in killing of *M. tuberculosis*. We also need to study the cross talk between SHP1 and cathelicidin. In chapter 4.2, we have identified *M. tuberculosis* cell wall lipid component keto-MA that binds to host TR4 and acts as ligand and induce IL10 expression. This cross talk assist in the survival of *M. tuberculosis* inside the host macrophage.

In chapter 5.1, we have identified the ligand binding residues of TR4 by *in-silico* studies and validated them by *in-vitro* transactivation luciferase reporter assay. In chapter 5.2, we have developed ONRLDB, a database of experimentally validated ligands of orphan NRs with all experimental values and structural information. We also incorporated several tools for user-friendly structural and scaffold analysis. We also made an attempt to generate AutophagySMDB, a database for small molecule modulators of autophagy.