SUMMARY AND FUTURE PERSPECTIVES

Over the past few years, many exceptional studies have broadened our horizons to understand the role of NRs and their regulatory pathways in immunological processes. The study discussed above extensively looked at the NRs expression profiles and highlighted their importance in immune regulation by DCs, rheumatoid arthritis and *M. tuberculosis* infection. In the first objective, we generated a comprehensive expression atlas of NRs in activated and tolerogenic DCs and characterized Nr4a2 in DC mediated tolerance. The immediate goal now is to explore the role of other intriguingly changing NRs in DC functionality. However, picking up and defining individual NRs may prove to be an exhaustive effort and hence calls for developing new and simple high-throughput assays that can successfully mark the role of a NR in particular DC function. It is also important to look at the changing lipid repertoire in activated vs. repressed state of DCs in terms of describing differential NRs activity when changes in expression is not a noteworthy phenomenon. It is also intriguing to test the effects of various cognate ligands of NRs on DC biology. Additional experimental work is required to correlate these findings in DCs isolated from human samples. Though we have established the role of Nr4a2 in DC tolerance, it might be worth probing how upstream signaling events regulate the activity of Nr4a2 in the absence of an endogenous ligand.

In the second objective, we monitored the levels of NRs in the initiation of disease progression and the full-blown disease. Currently, we are evaluating the possibility that NRs that are increased in the initial days of the disease progression prior to the actual symptoms of RA set up as biomarkers to identify people that are at increased risk of developing active RA. Most of the therapeutic drugs that are currently given to patients with RA targets either the cytokines or signaling events they initiate. These strategies though useful can't achieve complete remission from RA and hence requires indication of new therapies. Our expression

analysis can provide the basis for testing the ligands for NRs that are changing in the course of RA.

In the third objective, we observed that *M. tuberculosis* induces changes in the expression of NRs in both DCs and macrophages. Examining NRs of immune cells as part of a network rather than exploring the interactions of individual type of immune cells with the bacteria might be appealing. It is compelling to identify those NRs that affect the intracellular survival of the bacteria and to examine the potential of their ligands as an approach to anti-TB therapy. Testing of NR ligands in combination with existing drug regimen may reduce the time a patient has to on drugs and thereby increase the compliance for the TB therapy. Moreover, these ligands can also be tested as an effective therapy against MDR and XDR bacteria.