Summary

Native microbial squad of the gastrointestinal tract plays a crucial role in maintaining homeostasis in the host gut. Gut microbiome plays a central role in modulating metabolic disorders, hematopoiesis, prevention of enteric infections, etc. Despite ample awareness on the interface between the gut microbiota and the host immune response, it is still ambiguous whether these commensals can influence the immunological response and the survival of pathogens at systemic sites. The generation of enduring immunity by vaccines to protect against the pathogens is of utmost importance. Intriguingly, the efficacy of the vaccines is not uniform and varies across the globe. This scenario is highly evident in the case of BCG vaccine in TB-endemic and non-endemic countries, where its protective efficacy varies from 0% to 85%, respectively. Likewise, gut microbiome is extremely inconstant amongst the individuals. This made us to speculate whether the gut microbiome might be an important player in modulating the potency of vaccines. Consequently, in the current study, we monitored the impact of gut microbiota on modulating the pool of memory T cells in BCG vaccinated mice.

Interestingly, we observed impairment in the generation, sustenance and protective efficiency of memory CD4 T cells and CD8 T cells against *Mtb* in BCG vaccinated animals. Further, inhibition in the cytokine secretion and proliferation of *Mtb* specific T cells was noted. Most importantly, better survival of *Mtb* was noticed. We propose that

the alteration of gut microbiota can be one of the important factors in imparting inconsistency in the protective efficacy of BCG in protecting against TB globally.

Dendritic cells (DCs) play a vital role not only in the initiation of primary immune responses but also act as a bridge between innate and adaptive immunity by activation of naïve T cells. The role of gut microbiota in modulating the immune system is well known. However, nothing is precisely reported about the role of gut dysbiosis during the differentiation of DCs. Consequently, in our study (chapter 2), we investigated the effect of gut dysbiosis on the functionality of BMDCs and its subsequent ability to activate innate and adaptive immunity. Abx mediated gut dysbiosis substantially hampered the differentiation of bone marrow precursor monocytes to DCs. In addition, the BMDCs differentiated from dysbiosis induced animals (AbxDCs) exhibited downregulation in the expression of costimulatory and maturation markers such as CD86, CD40 and CD83. In addition, subdued release of proinflammatory cytokines IL-6, IL-12, IFN-γ, IL-1β cytokines with concomitantly enhanced secretion of anti-inflammatory IL-10 was observed. Importantly, AbxDCs were less potent in curtailing the growth of intracellular *Mtb,* which was associated with inhibition in the nitric oxide production and autophagy induction. Moreover, AbxDCs were less efficient in antigen uptake and their classical role of activating the naïve T cells. Our study highlights the impact of gut dysbiosis on impairing the potency of DCs to curtail the growth of *Mtb.*

Summary

The precise mechanism of cross-talk between gut microbiota and BMDCs to implement this function is not clearly known. However, recent reports suggest that the metabolism of dietary fibers by gut microbes lead to an increased concentration of circulating short-chain fatty acids (SCFAs). These SCFAs might lead to an alteration in the bone marrow hematopoiesis. Similar mechanism might underlie the protection in our model of *Mtb* infection. The gut microbes that bolster the efficacy of BCG vaccine may have a strong bearing on the protective efficacy of the vaccine. One of the strategies may be to develop probiotics from such microbes. Consequently, our findings may pave a way in future to study the impact of probiotics developed from gut microbiome in improving the sustenance and protective efficacy of BCG induced memory T cells against TB. Further, this strategy may have an important implication in employing mixture of BCG and probiotics for shortening the dose and duration of the TB drug regimen.