In view of the previous reports, which revealed the importance of MCP-1 at protein level and its two single nucleotide polymorphism -2518A/G and -362G/C in tuberculosis, the present study was done to find out the role of these SNPs and MCP-1 in tuberculosis and leprosy patients in Indian scenario.

The findings of our study showed that both -2518A/G and -362 G/C polymorphism is present in the studied population of Agra region. Statistical analysis showed that G/G genotype of -2518A/G polymorphism is associated with tuberculosis, as reported earlier in several reports, while A/G genotype shows association with healthy controls, but no difference at the allele level was observed. Similarly C/C genotype of -362G/C polymorphism shows association with tuberculosis while G/C genotype associated with healthy controls. Again, at the allele level, no difference was found. Haplotype A-C shows very strong association with tuberculosis. Serum MCP-1, IL-12p70 and TNF-α were found higher in PTB cases compared to controls. MCP-1 level was found higher in A/A genotype PTB cases, compared to G/G genotype, at both in vivo and in vitro experiments. Significant positive correlation was observed between MCP-1 and other cytokines at both in vivo and in vitro experiments in PTB cases, but not in healthy controls indicates role of MCP-1 in immune response against *M. tb*. Such correlation was not observed at genetic level, which indicates that MCP-1 might have some role in immune response against *M. tb* infection but MCP-1 gene polymorphism -2518A/G not have any direct impact on the immune response.

All the chemokine genes were expressed more in PTB cases as compared to controls in normal unstimulated condition, indicating the involvement of these chemokines during active tuberculosis.

Our study is probably the first report to show the role of MCP-1 gene polymorphisms in leprosy. Results indicate no association of -2518A/G polymorphism with leprosy at the genotype and allele level. The C/C genotype of -362G/C polymorphism was found to be associated with leprosy cases, while G/C genotype shows association with healthy controls. No association of both the polymorphisms were observed with RR and ENL
reactional leprosy cases, compared to normal leprosy cases. A-C and G-G haplotypes show strong association with healthy controls.

The levels of serum MCP-1, IL-12p70, TNF-α and TGF-β were found significantly high in leprosy cases as compared to controls, a reverse result was found for IFN-γ. MCP-1 level was found high in A/A genotype leprosy cases compared to G/G genotype, in controls, the result was reverse. MCP-1 showed negative correlation with IL-12p70 and positive correlation with TGF-β. The results were not reproducible in the in vitro experiments done in PBMCs of leprosy cases and controls, as observed in serum. RNA expression studies also did and not support the results of in vivo cytokine results. Although, the study revealed that all chemokine genes were expressed in less quantity in leprosy cases compared to healthy controls, indicating a defective immune response in leprosy cases.

EMSA and MALDI-TOF experiments revealed that a transcription factor Zinc finger protein binds to the sequences contains A and G polymorphic sites. Since this transcription factor binds to both the sequences, we conclude that the reason behind the overproduction of MCP-1 in A/A genotype subjects in our study and in G/G genotype subjects in several earlier studies, is not related to transcriptional regulation of the -2518A/G polymorphic site.

Basing on the reported evidences on important role of MCP-1 during infection, this study was initiated. Conflicting reports from various studies from worldwide population inspired us to look at the role of MCP-1 in genetic level as well as at protein level in our native population in India. Our study is presumably the first one to address the importance of MCP-1 polymorphisms in leprosy in India. Though two reports were available in India regarding the association with TB our study focused on northern Indian population of Agra and nearby regions. Further, our study attempted to associate the protein and RNA expression level alongwith genotypes in this population. We also analysed the production of related cytokines which are likely to influence the MCP-1 production and vice versa.

We could establish a significant link between the level of MCP-1 production with specific MCP-1 genotype. However the regulation of disease process /pathogenesis along with other cytokines could not be established. Since, TB being a multifactorial disease, it
is possible that other factors which we have not included in this study may be regulating the disease process along with MCP-1 after *M.tb* infection. Although the mechanism of MCP-1 transcription was partially understood before, for the first time we detected a zinc finger protein which bound to the -2518A/G site when cells were stimulated with mycobacterial antigens. This needs further indepth investigation to find out the exact role in protein/transcription level during the disease process. Finally our study has provided better insight into role of MCP-1 gene and protein in two important mycobacterial diseases in north Indian population. The observations have raised more questions, which warrant further investigations in selected cohorts of healthy persons and also patient populations followed over a period of time to understand the significance of these genotypes with disease process and protection.