Details of the Project sanctioned under the Human Resource Development scheme of Department of Health Research

1. **Project Title:** Proteomic analysis and immune properties of exosomes released by macrophages infected with *Mycobacterium tuberculosis*

2. Category of fellowship: Women Scientist

3. PI (Name & Address): Dr. Sonam Grover, Kusuma School of Biological Sciences, IIT Delhi-110016

4. Qualifications: PhD

5. Mentor or Co.PI (Name & Address): Prof. Seyed E. Hasnain, Kusuma School of Biological Sciences, IIT Delhi-110016

6. Duration of the project: Three Years

7. Broad area of Research: Proteomics

8. Summary of the Project: (Give in about 300 words)

Mycobacterium undergoes reductive evolution with the ancestors losing some genes and gaining few others enabling their survival in the intracellular environment in host and pathogenicity (1,2). Genome reduction further induces a genetic imprisonment upon the functional diversity of the resulting proteome. Such a genetic imprisonment on the functional proteome can be overcome by the use of post translational modifications (PTMs) as multiple PTMs can impart multiple functions to the same proteins. PTMs also play important role in immune modulation through antigen masking, alteration of antigen presentation and immune-regulation (3-5). *Mycobacterium indicus pranii (MIP)* is a nonpathogenic, saprophytic and fast growing mycobacterium (6). It has been used as a successful commercial immunotherapeutic vaccine 'Immuvac' against leprosy (7). Further, in animal models *MIP* has been found to be protective against tuberculosis infection and has been approved for human clinical trials (8). This broad spectrum vaccine potential may lie in the fact that *MIP* shares B and T cell antigens with other mycobacteria including *M. tuberculosis* and *M.*

leprae (9,10). Live *MIP* has been found to be more effective than heat killed *MIP* in providing immunity against tuberculosis in guinea pig model (8). This difference of efficacy might be related to the ability of live *MIP* to secret antigens in exosomes which are the secreted vesicle from various eukaryotic cells including immune cells into the extracellular space. Exosomes have been found to contain the components of the cells from which they are released i.e. exosomes from antigen presenting cells contain MHC-I, MHC-II and CD86 (11). Further, exosomes from *M.tb* infected cells have been found to contain various TB secreted antigens over the time (12). Exosomes released from mycobacterial-infected macrophages could be a trigger to activate both the innate and acquired immune responses *in vitro* and *in vivo* (13). Differences of PTMs between *MIP* and pathogenic mycobacteria may be a reason for the better antigenicity of this vaccine which can be exploited further. Thus, post translational modifications of secreted antigenic proteins of *M.tb* might play a very crucial role in host-pathogen interaction in the immune particularly in the immune context. Study of role of such PTMs can be utilized to develop new strategies to combat tuberculosis infection.

9. Objectives of the Proposal:

The overall aim of the study is to understand the role of post translational modifications of mycobacterial proteins in immunomodulation during the host pathogen interaction.

10. Innovations in the project: (Give in about 100 words)

The projects involves post translational modification analysis of secreted proteins of *M.tb* which has not been explored so far. Furthermore it will provide an new insight into the host pathogen interactions by the means of post translational modifications.

11. Significance of the outcome of the project: (Give in about 150 words)

The proposed studies on PTMs of *M.tb* will help in determining and establishing the function of the PTMs in the infection biology and immune evasion of *M.tb*. As PTMs are linked to antigen masking, their inhibition might act as an immunotherapeutic strategy to treat TB. This study on

type of PTMs will help to reveal the causative enzymes which can be targeted to design effective therapies against TB. Further, this study might highlight the importance of PTMs in the antigenicity of a vaccine which can be utilized to make more effective vaccines.

12. Relevance in Public Health:

Tuberculosis (TB) is one of the leading cause of human death by *M.tb* infection, despite the availability of curable drugs for more than decades. This medical-social problem stems in part from using anti-bacterial drugs that are principally active against replicating bacteria. In actual scenario a population of these bacteria are not replicating during infection, hence the treatment is ineffective. However, less than 10% of the infected individuals actually develop active disease and in >90% individuals, *M.tb* persists for years in a metabolically inactive, asymptomatic latent form. However, reactivation of latent TB, either due to malnutrition, immuno-suppression, or HIV co-infection account for the majority of active TB cases. The major problems with regard to TB are i) lack of proper diagnosis; ii) unavailability of efficacious vaccine iii) nexus with HIV is further aggravating the problem. Thus understanding of post translation modifications of *M.tb* will help in understanding the novel modes of host pathogen interactions and doveloping new strategies for combating TB.

Sonam Grover

Signature of the Fellow /Faculty