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

1. Project Title: "Identification of novel inhibitors of the N- acetylglucosamine-1-phosphate uridyltransferase (GlmU) in Mycobacterium tuberculosis".

2. Category of fellowship: HRD fellow start up project

3. PI (Name & Address): Dr. Inshad Ali Khan

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4. Qualifications: MSc, PhD

5. Mentor or Co.PI (Name & Address): NA

6. Duration of the project: 3 Years

7. Broad area of Research: COMMUNICABLE DISEASES

7.1 Sub Area: TUBERCULOSIS

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

Tuberculosis (TB) is one of the common and deadly infectious diseases caused by mycobacteria, mainly *Mycobacterium tuberculosis*. Because of the quiescent form of *Mycobacterium tuberculosis* strains, numerous current frontline therapeutics has become ineffective by the imminent exigency of multidrug-resistant. The bacterial GlmU protein, involved in peptidoglycan and lipopolysaccharide biosynthesis, has recently been identified as an important drug target. The *GlmU* has been identified as essential for optimal growth of *M. tuberculosis*. GlmU is a bifunctional acetyltransferase/uridyltransferase enzyme that catalyses the conversion of glucosamine-1-phosphate (GlcN-1-P) and acetyl coenzyme A (Acetyl CoA) to N-acetyl-glucosamine-1-phosphate (GlcNAc-1-P) and coenzyme A (CoA) at the C-terminal (acetyltransferase) domain followed by conversion of GlcNAc-1-P and UTP to UDP- N-acetyl-glucosamine (UDP-GluNAc) at the N-terminal (uridyltransferase) domain. The second step is present in both, bacteria and humans, where as the first step is present only in bacteria, which makes the first step a suitable target for designing non-toxic inhibitors. The

institute has a library of ~50,000 compounds (both acquired as well in house). This library has been screened against *M. tuberculosis* and about 1000 compounds active against *M. tuberculosis* have been identified. Herein, we propose to screen these active compounds against the acetyltransferase activity of GlmU protein At the same time in-silico docking approach will be used on the complete library of compounds to identify the potential inhibitors. Additionally, we will also screen another set of library of natural compounds against acetyltransferase activity of GlmU protein. *In-vitro* ADME and cytotoxicity profiling of identified inhibitors will be done to identify the hit compounds.

9. Objectives of the Proposal:

- Identification of novel GlmU inhibitors through screening of whole cell active compounds against *M. tuberculosis*.
- Identification of novel GlmU inhibitors through screening of natural compounds library.
- Identification of novel GlmU inhibitors through in-silico docking approach followed by wet lab validation.
- *In-vitro* and *ex-vivo* profiling of the identified inhibitors.
- *In-vitro* ADME and cytotoxicity profiling of identified inhibitors to select the hit compounds.

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

The project is aimed at applying multiple approaches such as whole cell active compounds, natural compounds and in-silico approach to identify novel GlmU inhibitors. Screening of natural compounds library will give us an opportunity to identify to first time identify the GlmU inhibitor/s from microbial or plant source. The identified inhibitors will profiled for in-vitro ADME and cytotoxicity to select metabolically stable and safe chemical structures for lead optimization.

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

Emergence of MDR and XDR clinical isolates of *Mycobacterium tuberculosis* has necessitated the urgent need for developing new targets which can circumvent the drug resistance. GlmU is one such essential target protein which is involved in peptidoglycan and lipopolysaccharide biosynthesis. GlmU is a bifunctional acetyltransferase/uridyltransferase enzyme that catalyses the conversion of glucosamine-1-phosphate (GlcN-1-P) and acetyl coenzyme A (Acetyl CoA) to N-acetyl-glucosamine-1-phosphate (GlcNAc-1-P) and coenzyme A (CoA) at the C-terminal (acetyltransferase) domain followed by conversion of GlcNAc-1-P and UTP to UDP- N-acetyl-glucosamine (UDP-GluNAc) at the N-terminal (uridyltransferase) domain. The second step is present in both, bacteria and humans, where as

the first step is present only in bacteria, which makes the first step a suitable target for designing non-toxic inhibitors. The expected outcome of the project is the identification of novel chemical scaffolds from the library of compounds as GlmU inhibitors which have good in-vitro ADME profile and are safe. These selected inhibitors can serve as starting point for medicinal chemistry optimization to develop lead compounds as drug candidates.

12. Relevance in Public Health:

Tuberculosis (TB) is one of the common and deadly infectious diseases caused by mycobacteria, mainly *Mycobacterium tuberculosis*. Because of the quiescent form of *M tuberculosis* strains, numerous current frontline therapeutics has become ineffective by the imminent exigency of multidrug-resistant and XDR clinical isolates. There is an urgent need for developing new targets which can circumvent the drug resistance and offer a better therapeutic outcome.

1/4/16

Signature of the Fellow /Faculty

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