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

1. **Project Title:** Evaluation of possible role of SHP-1 in obese insulin resistant murine model using fluorescence resonance energy transfer (FRET) approach

2. **Category of fellowship:** Start up research proposal

3. **PI (Name & Address):** **Dr. Farah Khan,**
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4. **Qualifications**: Ph.D [Biochemistry]

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6. **Duration of the project:** 3years
7. **Broad area of Research:** Immunology

7.1 Sub Area: Insulin resistance

8. Summary of the Project

The insulin signaling cascade is a network comprised of various kinases and phosphatases that act in an antagonistic way to maintain the steady state of insulin action. In obesity induced insulin resistance, this balance gets disturbed due to the action of pro-inflammatory molecules released from obese adipose tissue. These pro- inflammatory molecules interfere with the normal phosphorylation and dephosphorylation process of the members of insulin signaling pathway and leads to insulin resistance. Since phosphorylation-dephosphorylation is the major process by which insulin signaling is manifested, phosphatases represent a class of potential therapeutic target for obesity induced insulin resistance or type2 diabetes. One of such promising target is SHP-1[a src homology 2 domain containing tyrosine phosphates]. The role of this enzyme in negatively regulating the cytokine signalling, immunoreceptor transduction pathway, growth factor etc. has been well characterized, but little is known about the metabolic

action of this phosphatase on the insulin targeted tissue. The expression of SHP-1 is upregulated in the metabolic tissue such as skeletal muscle, white adipose tissue and liver of diet induced obese mice. Recently, it has been reported that mice which express low levels of catalytically impaired SHP-1 protein (viable motheaten mice) are highly insulin sensitive and glucose tolerant, the improved insulin sensitivity results from enhanced insulin receptor signaling to PI3K/Akt pathway. Also, mice lacking hepatocyte specific SHP-1 show improved whole body glucose homeostasis. This makes SHP-1 a potent mediator of diet induced insulin resistance through impairment of insulin receptor signaling for glucose metabolism and makes it a novel therapeutic target for obesity associated metabolic syndrome.The techniques so far employed to study the role of SHP-1 in insulin targeted tissue, are limited to in vitro study only, making the investigation of in vivo changes a difficult task. The need to study biochemical events occurring inside living cells has begun to yield a newly developed technique represented by a growing family of genetically-encodable FRET-based biosensors (fluorescence resonance energy transfer) which provides the spatial and temporal details of protein and protein-protein interaction.

9. Objectives of the Proposal:

SHP-1 is thought to play an important role in glucose homeostasis and inflammation. To analyze the effect of SHP-1 in inflammatory conditions as developed in obese insulin resistant murine model, following objectives are proposed:

1) To develop FRET based genetically encoded activity reporter for SHP-1.

2) To study the role of SHP-1 in obese insulin resistant murine model.

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

The present project proposes to evaluate the role of SHP-1 in development of insulin resistance in high fat diet fed murine model using FRET approach. Genetically-encodable FRET-based biosensor (fluorescence resonance energy transfer) which provides the spatial and temporal details of protein and protein-protein interaction is an innovative methods to study biochemical events occurring inside living cells. The biggest advantage of using FRET technology is that time lapse changes can be observed in a non invasive manner. Its sensitivity makes it the best technique that can be used in the current scenario as the changes in protein conformation are very quick and hence moment of capture should be precise.

11. Significance of the outcome of the project:

SHP-1 represents a recent target for design of drugs to ameliorate insulin resistance and type 2 diabetes. FRET based genetically encoded activity reporter for SHP-1 may be helpful in understanding its signalling cascade in High fat diet induced insulin resistance **and in future this activity reporter may be used for high throughput screening of anti-diabetic and anti-inflammatory drugs.**

12. Relevance in Public Health:

Novel mechanistic approaches to decipher the role of inflammation in obesity are the need of time and are being highly researched. Large-scale studies on obesity have already highlighted the marked alteration in expression of genes coding for proteins involved in inflammatory processes . Obesity is the epidemic of the 21st century. The World Health Organization estimated that in year 2008, globally 1.4 billion adults, 20 and older, were overweight [body mass index (BMI in kg/m^2) > 27]. Of these over 200 million men and nearly 300 million women were obese [BMI >30]. 65% of the world's population live in countries where overweight and obesity kills more people than underweight (WHO, 2014). The need to study biochemical events occurring inside living cells has begun to yield a newly developed technique represented by a growing family of genetically-encodable FRET-based biosensors (fluorescence resonance energy transfer) which provides the spatial and temporal details of protein and protein-protein interaction. FRET based genetically encoded activity reporter for SHP-1 may be helpful in understanding its signalling cascade in High fat diet induced insulin resistance **and in future this activity reporter may be used for high throughput screening of anti-diabetic and anti-inflammatory drugs.**

Signature of the Fellow /Faculty