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

1. Project Title: To investigate the role of autophagy in *Aspergillus fumigatus* pathogenesis.

2. Category of fellowship: Fellowship to women scientists with a break in career

Category A

3. PI (Name & Address): Dr Manu Goyal

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4. Qualifications

Degree/ Examination	Year	Name of the School/College/ University	Aggregate marks obtained	Distinction in subjects	Subjects of thesis if any
Matric	1996 CBSE	General Gurnam Singh Public School, Sangrur, Pb.	76%		
10+2	1998 PSEB	Govt. Ranbir College, Sangrur, Pb.	58.2%		
B.Sc.	2002 Punjabi University	Govt. Ranbir College, Sangrur, Pb.	69.3%		
M.Sc. Microbiology	2005	Punjab Agricultural University,	7.55/10		Effect of *Azorhizobium caulinodans* and phyto-hormones on

		Ludhiana, Pb.			para-nodulation, establishment and yield of rice
Ph.D.	2011	Post Graduate Institute of Med. Education & Research, Chandigarh	Degree awarded		*In vitro* molecular interaction between eukaryotic cells and clinical isolates of *Haemophilus influenzae*

5. Mentor or Co. PI (Name & Address): Dr. MEENU SINGH, Professor,

Advanced Pediatric Centre,

PGIMER Chandigarh

6. Duration of the project: Three years

7. Broad area of Research: Biotechnology

7.1 Sub Area: Cellular Microbiology

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

Aspergillus fumigatus is a ubiquitous saprophytic fungal pathogen responsible for a range of pulmonary diseases depending on immune status of the host. In the hypersensitive host, it can initiate an allergic response leading to Allergic Bronchopulmonary Aspergillosis (ABPA). The precise mechanism that makes *Aspergillus* an important pathogen in lungs is not yet fully implicit. For deeper understanding of host fungal interplay, the experimental conditions such as the oxygen concentration have to be adjusted to the reality of the infected lung tissue. In a given tissue microenvironment, oxygen availability is described as anaerobic, hypoxic (1.5% and lower) or normoxic (21%). Recent studies suggested that hypoxia occur *in vivo* in the lung during *A.fumigatus* infections. The small size of *A.fumigatus* conidia (2µm) permit them to reach the innermost areas of the lung, i.e. alveoli and proceed to germinate. The alveolar epithelium consists of type I and type II cells. Type I pneumocytes was initially believed to serve only simple barrier functions. More recently, type I cells have been implicated in a wide range of functions including lipid metabolism, cell signaling and host defense. Type I pneumocytes may play a vital role in the pathogenesis of *A.fumigatus* which has not been investigated earlier. However, *A.fumigatus* conidia

efficiently internalize in bronchial & alveolar cells and macrophages and germinate in acidic compartment. Recently, autophagy has emerged as a central component of the innate and adaptive immune responses and plays role in direct and indirect killing of intracellular and extracellular pathogens including fungi. *A. fumigatus* infection of human monocytes triggered selective recruitment of autophagy protein LC II in phagosomes (Kyrmizi *et al*, 2013). The aim of this study is to investigate the contribution of autophagic pathway to the clearance of *A.fumigatus* from bronchial and alveolar epithelial cells (type I & type II); and alveolar macrophages under hypoxic conditions.

9. Objectives of the Proposal:

1) To establish *Aspergillus fumigatus* infection in bronchial (BEAS-2B) and alveolar epithelial cells- Type I- (WI-26) and Type II (A549); and primary alveolar macrophages under hypoxic conditions.

2) To determine the involvement of various autophagic molecules/markers during the course of *A.fumigatus* infection.

3) To evaluate the effect of topical steroids on autophagic molecules/markers involved during the course of *A.fumigatus* infection.

4) To assess the impact of inhibition / induction of autophagy on *A.fumigatus* infection by use of pharmacological modulators (inhibitor/inducer) of autophagy.

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

At present no evidence is available about the involvement of autophagic machinery in relation to *A.fumigatus* interaction with nonprofessional phagocytes- i.e. bronchial and alveolar epithelial cells in host defense under hypoxic conditions. In the present study, an attempt will be made to investigate the contribution of autophagic pathway to the clearance of *A.fumigatus* from bronchial and alveolar epithelial cells; and alveolar macrophages.

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

Although substantial amount of information concerning anti-bacterial and anti-viral host defence mechanisms are available, limited data subsist in the field of fungal interactions. This

study will aim toward understanding the potential impact of how *Aspergillus fumigatus* hypoxic response affects the killing and clearance of infection by cells of innate immune system. Also, this study will signify the role of autophagic pathway in antifungal immunity and impact of immunomodulation strategies of autophagic pathway (inhibition or stimulation) on ABPA pathogenesis.

12. Relevance in Public Health:

A comprehensive understanding of the autophagic machinery in *A.fumigatus* and Allergic Bronchopulmonary Aspergillosis pathogenesis will provide a rational basis for the design of new antifungal drug targets and development of potential therapeutic interventions to improve outcome in patients who are at risk for bronchopulmonary infections.

Manu Goyal

Signature of the Fellow /Faculty