f. A signed statement by the applicant that the research work under reference has not been given any award. The applicant should also indicate the extent of the contribution of the others associated with the research and he/she should clearly acknowledge his/her achievements (Max: 500 KB)

The nomination for 'SUN PHARMA SCIENCE FOUNDTION RESEARCH AWARDS - 2021 in the area of Medical Sciences – Basic Research is made based on research work described below.

Dr Mukhopadhyay has made immense and excellent contribution in 'Disease Biology' with a focus to understand molecular mechanism of pathogenesis in Tuberculosis (TB) based on her studies in in vitro cell culture, animal model and in clinical settings. She has identified that ESAT-6 protein of *Mycobacterium tuberculosis* inhibit or delay CD8 T cell function which is known to be protective against tuberculosis as well as increase intracellular iron level in macrophages (important for intracellular multiplication of the bacteria) by directly interacting with Beta-2 microglubulin (β2M) molecule in macrophages (published in *PLOS Pathogens* (2014)10:e1004446 [114 citation]). Based on these findings, next she identified two FDA approved drugs (Mirabegron [SM09] and Olsalazine [SM15]) that target ESAT-6-β2M interaction and showed promising therapeutic results (*Journal of Immunology* [2019] 203:1918; *Journal of Immunology* [2020] 205:3095). This work ushers promising approaches for host directed immune therapy targeting ESAT-6, to increase host protective responses against TB. The study will make a long term contribution in preventing infection and disease in countries with high burdens of TB.

Two main Publications

1. Jha V, Pal R, Kumar D and **Mukhopadhyay S*** (2020). ESAT-6 protein of *Mycobacterium tuberculosis* increases holotransferrin mediated iron uptake in macrophages by downregulating surface hemochromatosis protein HFE. ***Journal of Immunology*** 205: 3095-3106 (Impact factor – 5.4)

***Corresponding Author**

Achievements of Dr. Mukhopadhyay: It is known that *Mycobacterium tuberculosis* recruit holotransferrin at the surface of the phagosome. But the upstream mechanism by which it modulates holotransferrin-mediated iron uptake at the surface of macrophage is not well understood. Accessibility of iron at the phagosomal surface inside macrophage is crucial for survival and virulence of *M. tuberculosis*. Dr. Mukhopadhyay for the first time report that interaction of the ESAT-6 protein of *M. tuberculosis* (ESAT-6 is absent in BCG, the vaccine strain of Tuberculosis) with β2M causes downregulation of surface HFE, a protein regulating iron homeostasis via interacting with transferrin receptor 1 (TFR1). She explained that ESAT-6:β2M interaction leads to sequestration of HFE in endoplasmic reticulum, causing poorer surface expression of HFE and HFE:TFR1 complex (nonfunctional TFR1) in peritoneal macrophages from C57BL/6 mice, resulting in increased holotransferrin-mediated iron uptake in these macrophages. This favors better survival of the bacilli inside macrophages.

As Principal investigator and Corresponding author, Dr. Mukhopadhyay was involved in proposing the idea, designing, and overall execution of the project. She was also involved in guiding students, analyzing data, writing and communicating manuscripts in *Journal of Immunology*. All experiments were carried out in Dr. Mukhopadhyay's laboratory at CDFD, Hyderabad. She collaborated with Dr. Dhiraj Kumar, New Delhi for *M. tuberculosis* infection work at BSL3 Laboratory of ICGEB, New Delhi where her student Dr Jha has performed all the experiments (as CDFD, Hyderabad does not have functional BSL3 laboratory).

2. Jha V, Rao RN, Janardhan S, Raman R, Sastry GN, Sharma V, Rao JS, Kumar D and **Mukhopadhyay S*.** (2019). Uncovering structural and molecular dynamics of ESAT-6:β2M interaction: Asp53 of human β2-microglobulin is critical for the ESAT-6:β2M complexation. ***Journal of Immunology*** 203: 1918-1929 (Impact factor – 5.4)

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Achievements of Dr. Mukhopadhyay: In this study Dr. Mukhopadhyay has identified the detail ESAT-6:β2M complexation and reported two FDA approved drugs (Mirabegron and Olsalazine) which inhibit binding of β2M to ESAT-6. This results in increased MHC class I antigen presentation which was correlated with decreased survival of the bacilli. Thus Mirabegron and Olsalazine can be successfully repurposed as anti-tuberculosis drugs either as a standalone therapy or as an adjunct to current DOTs based regime against *M. tuberculosis*

As Principal investigator and Corresponding author, Dr. Mukhopadhyay was solely involved in proposing the idea, designing and overall execution of project. She was also involved in guiding students, day to day execution of the research work, analyzing data, writing and communicating manuscript in *Journal of Immunology*. Dr. Mukhopadhyay's group has carried out the modeling of ESAT-6 and β2M in collaboration with Dr. G.N. Sastry's group from IICT, Hyderabad. She collaborated with Dr. D. Kumar, New Delhi for *M. tuberculosis* infection work as CDFD, Hyderabad does not have functional BSL3 laboratory. Since CDFD does not have high quality ITC and MST instruments, Dr. Mukhopadhyay has collaborated with Dr. R. Raman and Dr. J.S. Rao to execute ITC and MST experiments. Dr. R.N. Rao from Dr. Mukhopadhyay's group has performed the ITC and MST experiment under their guidance.

This is to state that the above research work published has not been used for applying any award in the past.

Signature:
Name: Sangita Mukhopadhyay
Date: 24.09.2021

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