**Statement of Research Achievements, if any, on which any Award has already been Received by the Applicant. Please also upload brief citations on the research works for which the applicant has already received the awards (Max. 1 MB)**

Dr Dwivedi along with his colleagues provides evidence for the first time that Th17 cell responses in the lung play a critical role for enhanced protection against TB. Surprisingly, They provide evidence that the ESAT-6 protein, which is absent in BCG but present in H37Rv, induces IL-6 and TGF-β in dendritic cells in a TLR-2 and MyD88-dependent manner, which generates an environment that is conducive for the differentiation of Th17 cells in the lung. Their findings indicate that, in addition to Th1 cells, Th17 cells play a critical role in conferring optimal protection against TB **(PLoS Pathogens 2011)**.

Furthermore, Dr Dwivedi first time showed that IL-1β, produced by phagocytes infected by virulent *M.tb* strain H37Rv, directs Th2 cell differentiation. In sharp contrast, the vaccine strain Bacille Calmette-Guérin as well as RD-1 and ESAT-6 mutants of H37Rv failed to induce IL-1β and promote Th2 cell differentiation. Furthermore, ESAT-6 induced IL-1β production in dendritic cells (DCs), and $CD4^+$T cells co-cultured with infected DCs differentiated into Th2 cells. Taken together, their findings indicate that IL-1β induced by RD-1/ESAT-6 plays an important role in the differentiation of Th2 cells, which in turn facilitates progression of TB by inhibiting host protective Th1 responses **(Journal of Biological Chemistry 2012)**.

Dr Dwivedi and his colleagues showed that Thp5, a novel peptide with structural similarity to vasoactive intestinal peptide, regulates production of early IL-4 in newly activated $CD4^+$T cells. Induction of IL-4 in $CD4^+$T cells by Thp5 is independent of the transcription factor STAT6 but dependent on ERK1/2 signaling. They showed that Thp5 enhances Th2 responses and exacerbates allergic airway inflammation in mice. Taken together, their findings reveal that early activated $CD4^+$T cells produce Thp5, which plays a critical role as a molecular switch in the differentiation of Th cells, biasing the response toward the Th2 cell phenotype **(Journal of Biological Chemistry 2012)**.

Dr Dwivedi first time showed that $CD4^+$T cells from TGF-βRIIDN mice are resistant to Th17 cell differentiation and, paradoxically, that $CD8^+$T cells from these animals spontaneously acquire an IL-17-producing phenotype. Neutralization of IL-17 or depletion of CD8 T cells dramatically inhibited inflammation in TGF-bRIIDN mice. Therefore, the absence of TGF-β triggers spontaneous differentiation of IL-17-producing $CD8^+$T cells, suggesting that the *in vivo* and *in vitro* conditions that promote the differentiation of IL-17-producing $CD8^+$T cells are distinct **(Journal of Biological Chemistry 2012)**.

Dr Dwivedi along with his colleagues first time showed that miRNA-99b (miR-99b), an orphan miRNA, plays a key role in the pathogenesis of *M.tb* infection. Their findings unveil a novel host evasion mechanism adopted by *M.tb* via miR-99b, which may open up new avenues for designing miRNA-based vaccines and therapies **(Journal of Biological Chemistry 2013)**.

Dr Dwivedi along with his colleagues developed a novel therapy for tuberculosis as they show that animals (Stat-6$^{-/-}$CD4-TGFβRIIDN mice) that are unable to generate both Th2 cells and Tregs are highly resistant to *M.tb* infection. Furthermore, simultaneous inhibition of these two subsets of Th cells by therapeutic compounds dramatically reduced bacterial burden in different organs. This treatment was associated with the generation of protective Th1 immune responses. As these therapeutic agents are not directed to the harbored organisms, they should avoid the risk of promoting the development of drug-resistant *M. tuberculosis* variants **(Journal of Biological Chemistry 2014a)**.

Furthermore, they demonstrate that these drugs induce a shift in the development of T cell memory, favoring central memory T (Tcm) cell responses over effector memory T (Tem) cell responses. Collectively, their findings provide evidence that simultaneous inhibition of Th2 cells and Tregs during BCG vaccination promotes vaccine efficacy **(Journal of Biological Chemistry 2014b)**.

Dr Dwivedi and his colleagues reported that TlyA significantly contributes to the pathogenesis of *M.tb.* They show that a TlyA mutant *M.tb* strain induces increased IL-12 and reduced IL-1β and IL-10 cytokine responses, which sharply contrasts with the immune responses induced by wild type *M.tb*. Furthermore, compared with wild type *M.tb,* TlyA-deficient *M.tb* bacteria are more susceptible to autophagy in macrophages. Consequently, animals infected with TlyA mutant *M.tb* organisms exhibited increased host protective immune responses, reduced bacillary load, and increased survival compared with animals infected with wild type *M.tb*. Thus, *M.tb* employs TlyA as a host evasion factor, thereby contributing to its virulence **(Journal of Biological Chemistry 2015)**.

Dr Dwivedi and his colleagues showed that pharmacological inhibition of Kv1.3$^{+}$, a potassium channel preferentially expressed by Tem cells, with Clofazimine selectively expands Tcm cells during vaccination with Bacillus Calmette Guerin (BCG). Therefore, Clofazimine enhances Tcm cell expansion, which in turn provides improved vaccine efficacy. Thus, Kv1.3$^{+}$ blockade is a promising approach for enhancing the efficacy of the BCG vaccine in humans **(Journal of Infectious Diseases 2016)**.

Dr Dwivedi along with his colleagues showed that bergenin, a phytochemical isolated from tender leaves of *Shorea robusta*, activates the MAP kinase and ERK pathways and induces TNF-α, NO and IL-12 production in infected macrophages. They further

show that bergenin induces Th1 immune responses and potently inhibits bacillary growth in a murine model of *M.tb* infection. These findings suggest that bergenin might be an effective adjunct to ATT for patients with *M.tb* infection **(Frontiers in Cellular and Infection Microbiology 2017)**.

Dr Dwivedi was also involved in a collaborative project showing that ICAM-1 and ICAM-4 play roles in host cell invasion by *M. tuberculosis* and *P. falciparum*, respectively, either as receptors or as crucial accessory molecules **(Nature Communications 2015)**.

In another collaborative project Dr Dwivedi was involved to show that *Pf*TyrRs as a parasite-secreted protein that triggers pro-inflammatory host responses, along with its atomic resolution crystal structure in complex with tyrosyl-adenylate, provides a novel platform for targeting *Pf*TyrRs in anti-parasitic strategies **(Nature Communications 2011)**.

Furthermore, Dr Dwivedi established his own group, Immunobiology group at ICGEB, New Delhi in early 2019 and started giving training to his graduate students and post-doctoral fellows. One of his finding recently got published in The **Journal of Biological Chemistry 2019,** where his group has shown that immunomodulators, Bergenin, isolated from medicinal plants may be employed as an adjunct therapy along with traditional tuberculosis therapy with ATT therapy in mice. They observed that co-treatment with the anti-TB drug isoniazid and bergenin produces additive effects and significantly reduces bacterial loads compared with isoniazid treatment alone. The bergenin co-treatment also reduced isoniazid-induced immune impairment; promoted long-lasting, antigen-specific central memory T cell responses; and acted as a self-propelled vaccine. Of note, bergenin treatment significantly reduced the bacterial burden of a multidrug-resistant TB strain. These observations suggest that bergenin may be potent immunomodulatory agent that could be further explored as a potential adjunct to TB therapy **(Journal of Biological Chemistry 2019)**.

**CITATIONS:**

**Citation for BRICS Young Scientist Award 2022:**

Dr Dwivedi demonstrated that Th2 cells and Tregs inhibition and $Kv1.3^{+}$ blockade in T-cells promotes BCG vaccine efficacy. His research unveiled mechanistic details of TB pathogenesis such as the role of IL-1β induced by RD-1/ESAT-6 in Th2 differentiation and the role of mesenchymal stem cells as a long-term natural reservoir of dormant *Mycobacterium tuberculosis*.

**Citation for ICMR-Shakuntala Amir Chand Award 2020:**

The award for the year 2020 is being presented to Dr Ved Prakash Dwivedi, Group Leader, Immunobiology Group at International Centre for Genetic Engineering and Biotechnology, New Delhi for his outstanding contributions in unveiling the mechanistic details of Tuberculosis pathogenesis and host-protective immune responses. His group has developed several immunotherapeutic approaches for Tuberculosis treatment. His work also resulted in the generation of newer adjunct vaccines against Tuberculosis.

**Citation for NASI-Young Scientist Award 2019:**

Dr Dwivedi for first time provide evidence that ESAT-6, expressed by the virulent *M.tb* H37Rv but not by BCG, promotes vaccine enhancing Th17-responses. These activities of ESAT-6 were dependent on TLR-2/MyD88 signaling and involved IL-6 and TGF-β production by DCs. Collectively, in addition to Th1-immunity induced by BCG, RD1/ESAT- 6-induced Th17-responses are essential for optimal vaccine efficacy.

Place: New Delhi
Date: 29th August 2023

Signature of the Applicant