GENERAL AREA OF SCIENTIFIC INTEREST

During my research career, I tried to address fundamental issues pertaining to macrophage biology that have provided conceptual leads towards identification of novel and effective chemotherapeutic targets and formulations of better therapy against macrophage-associated diseases. I have used visceral leishmaniasis (VL) as model macrophage disease caused by the protozoan parasite, *Leishmania donovani*. In order to establish infection, intra-macrophage pathogens need to inhibit complex host defense signal transduction pathways culminating in the production of robust defence parameters including inflammatory cytokines, reactive oxygen and nitrogen species, inflammasome formation and apoptosis. I am trying to identify the key molecules and steps of macrophage signaling pathways manipulated by *Leishmania donovani* during various phases of infection to ensure their successful survival and replication. My research group is primarily interested in

1. **Identifying molecular events associated with the early phase entry of the parasite inside the host macrophages.**

Toll-like receptors (TLRs), which recognize pathogen-associated molecular pattern (PAMP), are the means for first line of host defense leading to pathogen clearance via enhanced pro-inflammatory response. However, this potent defense mechanism of the host cell puts strong selective pressure on *Leishmania* parasites, which have, in turn, evolved strategies to modulate the host TLR signaling cascade in their own favor. I tried to elucidate the molecular mechanisms associated with this down-regulation of TLR4 pathway in *L. donovani* infection and identified that the key molecule associated with this event is tumor necrosis factor receptor–associated factor (TRAF) 3, a negative regulator of TLR pathway (Gupta et al., *FASEB J*, 2014, **28**: 1756-1768.). Apart from TLR, another important host defense mechanism is to produce reactive oxygen species (ROS) to eliminate the pathogens. Our research showed that *Leishmania* inhibited mitochondrial ROS to neutralize inflammasome activation (Gupta et al., *FASEB J*, 2017, **31**: 5087-5101) and activate anti-oxidant enzyme heme oxygenase 1 (HO-1), which by degrading heme prevents maturation of major macrophage

2. **Identifying late phase host modulators exploited by the parasite for their successful survival and replication inside the hostile macrophage environment.**

After initial entry and down-regulation of immediate host activation, *Leishmania* needs specific molecules that are either secreted by it or may activate macrophages to produce immunosuppressive molecules that render the host defense inactive. Our study showed that late phase parasite survival requires PGE$_2$, a lipid mediator, which mediates its action by cAMP-dependent pathway and we have substantiated this hypothesis by both *in vitro* and *in vivo* inhibitor-based approach (Saha et al., *J. Immunol*, 2014, 193: 2330-2339). Furthermore, we have recently shown that the cAMP dependent pathway-mediated immunomodulation during infection by *Leishmania* is primarily executed through cAMP dependent protein kinase A (PKA), which consists of catalytic subunits C1 and C2 and regulatory subunits RI and RII. Specific substrate targeting of PKA is achieved by binding with scaffold proteins AKAP (A kinase-anchoring protein). Our detailed experimentation on the screening as well as the role of major AKAP proteins led to the observation that specific AKAPs associate with PKA during infection and revealed that *Leishmania*-induced immunosuppression was mediated by AKAP8-anchored PKA-RII for inflammatory cytokines and AKAP10-anchored PKA-RI subunit for inflammatory chemokines (Saha et al., communicated…..).

3. **Identifying anti-apoptotic proteins used by the parasite to subvert macrophage apoptotic machinery, thus establishing its replicative niche inside the host.**

One of the major host defense mechanisms against intra-macrophage pathogens is to facilitate pathogen clearance by apoptosis of the host cells. Conversely, pathogen tries to save its niche for replication and multiplication and thus critically turn off the host apoptotic machinery for the same purpose. Our study revealed that *Leishmania* parasite employs suppressor of cytokine signaling (SOCS) group of proteins to subvert macrophage apoptotic machinery through participation of thioredoxin and protein tyrosine phosphatase (PTP) (Srivastav et al., *J. Biol. Chem*. 2014, 289:1092-105). Subsequently we identified host protein myeloid cell leukemia 1 (MCL-1), which plays an important role in inhibiting mitochondria-dependent macrophage apoptosis. Our detailed work has shown that infection by *Leishmania* induced translocation of MCL-1 to mitochondria, where it interacts with the major pro-apoptotic protein BAK and prevents BAK-BAK homo-oligomer formation thereby preventing cytochrome c release mediated mitochondrial dysfunction. (Giri et al., *J. Biol. Chem.*, 2016, 291, 3496-3507).

4. **Identification of a single macrophage regulatory protein which prevents both immune activation and apoptosis, essential for parasite survival.**
*Leishmania* parasite dampens host defense mechanisms by regulating various parameters starting from modulation of cytokine and reactive oxygen and nitrogen species responses to inhibition of apoptosis. To modulate these various parameters it seemed appropriate for the parasite to take use of a master regulator thereby securing its niche with minimum effort. In our search for such a regulator, we came across with the identification of PI3K modulated AKT, whose role seems to be multifaceted. *Leishmania* exploits the master regulator AKT signalling in its favour by GSK-3β-mediated activation of β-catenin, an anti-apoptotic transcription factor, in one hand and by directly inactivating FOXO-1, a pro-apoptotic pro-inflammatory transcription factor, on the other hand thereby frustrating host cell defense (Gupta et al., *Cell Death Differ.* 2016, 23: 1815-1826).

5. **Role of immunomodulators as an intervention therapy.**
By way of immunomodulation therapy we have already shown the effective role of curdlan, a naturally occurring herbal immunomodulator that could completely cure experimental VL through significantly enhanced production of NO. Along with induction of disease-resolving Th1 cytokines, curdlan stimulates the production of IL-23, which helps in the stabilization and differentiation of Th17 cytokine, IL-17 (Ghosh et al., 2013, *J. Infec. Dis.*, 207: 1016–1025). Our work also led to developing 18β-glycyrrhetinic acid, a pentacyclic triterpene of licorice root, as highly effective anti-leishmanial agent, which has strong immunomodulatory potential for its use in general for macrophage-associated diseases (Gupta et al., 2015, Antimicrb. Agents Chemother. 59: 2531–2539; Ukil et al., PLoS ONE, e29062, 2011; Ukil et al., J. Immunol. 175: 1161-1169, 2005).

Our work thus provides important insights into the molecular mechanisms of how pathogens modulate macrophage defense signalling pathways to survive in phagocytes. Deciphering this intricate survival mechanism *Leishmania* has devised to frustrate the host defense system is a crucial contribution not only in understanding the biology of *Leishmania* but also suggests innovative target to arrest the infection process.

**AWARDS AND HONOURS**

- Invited by **French National Research Agency (ANR)**, Govt. of France to act as a reviewer in the panel “**CE15 - Immunologie, Infectiologie et Inflammation**” for evaluating the generic call for proposals 2019.

- Received **National Bioscience Award for Career Development** for the year 2016 from Department of Biotechnology (DBT).

- Received **AN Bhaduri award by SBC (I)** in 2017.
• Elected as Fellow in the National Academy of Sciences, India (FNASc) in 2017.

• Received Prof. B.K. Bachhawat Memorial Young Scientist Lecture Award by National Academy of Sciences, Allahabad, India (NASI) in 2014.

• Received SERB Women Excellence Award by Department of Science and Technology (DST) in 2013.

• Received Young Scientist Award in Biomedical Sciences by National Academy of Sciences, India (NASI) in 2010.

• Received Indo-Israel Collaborative Project entitled: "The roles of IL-17 and IL-23 in the protection against leishmania infection" funded jointly by The Israel Science Foundation (ISF) and the University Grant Commission (UGC) in 2016.

• Acted as reviewer in reputed peer-reviewed journals like FASEB Journal, Journal of Infectious Diseases, PLoS Neglected Tropical Diseases etc..

Students placements:

<table>
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<tr>
<th>Name of scholars</th>
<th>Designation</th>
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<tbody>
<tr>
<td>Dr. Kuntal Ghosh</td>
<td>National Post-doctoral Fellow at Dept. of Biochemistry and Biophysics, University of Kalyani</td>
</tr>
<tr>
<td>Dr. Jayeeta Giri</td>
<td>Research associate at Dept. of Medicine, University of Wisconsin, Madison, USA</td>
</tr>
<tr>
<td>Dr. Purnima Gupta</td>
<td>Post-Doctoral Fellow, Infections and Cancer Biology Group, International Agency for Research on Cancer, 69372 Lyon CEDEX 08, France</td>
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<tr>
<td>Dr. Amrita Saha</td>
<td>Research associate at Infectious diseases and Immunological Division, Indian Institute of Chemical Biology</td>
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<tr>
<td>Shriya Saha</td>
<td>Thesis submitted</td>
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<tr>
<td>Moumita Basu</td>
<td>Thesis submitted</td>
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Complete list of research publications:


**Books/book chapters :**


**Looking for highly motivated students with NET (CSIR/UGC/DBT/ICMR) preferably having sound knowledge in Biochemistry and Immunology.**