My research work is focused on the cell signaling networks in macrophages during various pathophysiological conditions that lead to inflammatory diseases. We study the basic biology of inflammation as well as the regulatory mechanisms that control the initiation, quality, and intensity of inflammatory responses. Our breakthrough discovery demonstrating the role of Neuronal Nitric Oxide Synthase (NOS1)-derived Nitric Oxide (NO) in turning on the inflammatory response during chronic inflammatory diseases (*J Exp Med, 2016*) is a turning point in NOS1 signaling. The discoveries lead investigators across the globe to understand and research macrophage NOS1-derived NO in the context of various chronic inflammatory conditions. Our recent work on Toll-interleukin-1 Receptor (TIR) domain-containing adaptor protein (TIRAP) emphasizes its central role in various inflammatory responses (*Frontiers Immunology; 2021)*. The varied interactions of TIRAP with its binding partners define the type of inflammatory response involved. The dynamic behavior of its interaction with its binding partners demonstrates the severity of the inflammation (*Frontiers Immunology; 2023*). Understanding TIRAP interactions is critical in understanding different chronic inflammatory conditions and therapeutic strategies to dampen the extent of acute and chronic inflammatory diseases.

Our group is actively involved in anti-inflammatory drug discovery projects. We repurposed drugs (*Gefitinib, Thioridazine, and Dorzolamide*) for their anti-inflammatory properties (*Sci Rep. 2018; Biomed Pharmacother. 2018; Future Med Chem., 2023*). The discovery of anti-inflammatory medicines was the product of a long-term investigation of mechanisms regulating inflammatory signaling. Our recent findings, demonstrate a novel combination of a broad-spectrum antibiotic Levofloxacin and a repurposed anti-inflammatory drug Dorzolamide (*A composition for sepsis and method thereof. TEMP/E-1/44471/2023- MUM*). We identified, Levofloxacin is not only a broad-spectrum antibiotic but also can control chronic inflammation in the host by inhibiting activation of Toll-interleukin-1 Receptor (TIR) domain-containing adaptor protein (TIRAP), which is necessary for the induction of major inflammatory signaling pathways (NF-KB and AP-1). Dorzolamide (DZD) has already been repurposed as an anti-inflammatory drug that targets TIRAP and eventually inhibits major chronic inflammatory pathways. The synergistic effect of both drugs has been proven efficacious in severe polymicrobial sepsis.

The studies will pave the path finding effective and potent therapeutic strategies for the treatment of various chronic inflammatory diseases including Sepsis, Asthma, Arthritis, Atherosclerosis, and others.

References:

1. Rajpoot S, Wary KK, Ibbott R, Liu D, Saqib U, Thurston TLM, BaigMS. TIRAP in the Mechanism of Inflammation. **Front Immunol.** 2021;12:697588. doi: 10.3389/fimmu.2021.697588. eCollection 2021. Review. PubMed PMID: 34305934; PubMed Central PMCID: PMC8297548.

2. Rajpoot S, Kumar A, Gaponenko V, Thurston TL, Mehta D, Faisal SM, ZhangKY, Jha HC, Darwhekar GN, Baig MS. Dorzolamide suppresses PKCδ - TIRAP-p38 MAPK signaling axis to dampen the inflammatory response. **Future Med Chem.** 2023 Apr 27;. doi: 10.4155/fmc-2022- 0260. [Epub ahead of print] PubMed PMID: 37129027.

3. Baig MS, Zaichick SV, Mao M, de Abreu AL, Bakhshi FR, Hart PC, Saqib U, Deng J, Chatterjee S, Block ML, Vogel SM, Malik AB, Consolaro ME, Christman JW, Minshall RD, Gantner BN, Bonini MG. NOS1-derived nitric oxide promotes NF-κB transcriptional activity through inhibition of suppressor of cytokine signaling-1. **J Exp Med.** 2015 Sep 21;212(10):1725-38. doi: 10.1084/jem.20140654. Epub 2015 Aug 31. PubMed PMID: 26324446; PubMed Central PMCID: PMC4577833.

4. Mirza S. Baig, Teresa Thurston, Rahul Sharma, Rajat Atre, Uzma Saqib, Rakhi Khabiya, Shreya Bharti and Chit L. Poh. Targeting Signalling Pathways in Inflammatory Diseases. **Frontiers Immunology**. 2023; 10.3389/fimmu.2023.1241440.

5. Baig MS, Roy A, Saqib U, Rajpoot S, Srivastava M, Naim A, Liu D, Saluja R, Faisal SM, Pan Q, Turkowski K, Darwhekar GN, Savai R. Repurposing Thioridazine (TDZ) as an anti-inflammatory agent. **Sci Rep.** 2018 Aug 20;8(1):12471. doi: 10.1038/s41598-018-30763-5. PubMed PMID: 30127400; PubMed Central PMCID: PMC6102213.

6. Srivastava M, Saqib U, Banerjee S, Wary K, Kizil B, Muthu K, Baig MS. Inhibition of the TIRAP-c-Jun interaction as a therapeutic strategy for AP1-mediated inflammatory responses. Int Immunopharmacol. 2019 Jun;71:188-197. doi: 10.1016/j.intimp.2019.03.031. Epub 2019 Mar 22. PubMed PMID: 30909134.