B. Personal Statement: My research is mainly focused on looking at different aspects of inflammation, mostly of the mucosal surfaces, and specifically in the context of clinical/recreational use of morphine. With this central theme, we look at several aspects of morphine-induced inflammation with the backdrop of secondary infection and HIV animal models as listed below:

1. Respiratory depression and lung inflammation are the major contraindications of morphine usage and disruption of interleukin (IL)-17 homeostasis has been implicated as one of the major reasons for this inflammation. Our studies have shown that chronic use of morphine disrupts IL-17A homeostasis in the lungs, resulting in low-level persistent inflammation in the context of opportunistic infections (pneumonia as a model) and/or HIV-1 (EcoHIV and HIV protein transgenic “Tg” murine models) as an additional insult. We are in the process of developing these animal models with the ultimate aspiration of testing interventions to bring down morphine-induced persistent inflammation in the lungs, which is one of the significant causes of morbidity (and sometimes, mortality) in HIV patients in the clinics, who are on opiates for pain management and most likely than not, also harbor opportunistic infections due to HIV/morphine-induced compromised immune system.

2. Chronic morphine has been shown to induce sepsis, mostly proceeding to septic shock in the context of secondary infections in animal models as well as in the clinics. This is a result of the abrogation of endotoxin tolerance, which otherwise, is a natural response of an organism to restore homeostasis after a protective pro-inflammatory phase. Among many factors responsible for maintaining the steady-state, we have recently described the microRNAs (miRs), directed against components of Toll-like receptor pathways, as molecular switches regulating this homeostasis. In normal conditions, infection results in up-regulation of miR-146a and miR-155, which then target specific components of the TLR pathways, resulting in their shutdown, thus effecting
endotoxin tolerance. We have seen preferential down-regulation of these miRs with chronic morphine, resulting in abrogation of tolerance and hyper-inflammation. We are currently using lentiviral reporters to further elucidate this phenomenon and find the molecular links between the μ-opioid receptor and the miRs/pro-inflammatory signaling intermediates.

3. The correlation between obesity induced tissue inflammation and its effects on insulin resistance and Type 2 Diabetes Mellitus (T2DM) is amply drawn in mice and human studies, the mechanism underlying the phenomena, however, is poorly understood. In human studies, the data is essentially end-point and not open to manipulations. Therefore, we set out to establish a “humanized” mice model, where we obtain subcutaneous and visceral adipose tissue from the lean and obese (and type II diabetic) patients and transplant them into immune-compromised NOD/SCID mice. Next, we inject the metabolically labeled leukocyte fraction from the same patient into the mice. Currently we are establishing the parameters to finally validate the model. Further studies would include morphine modulation of type II diabetes and intervention studies to reduce adipose tissue inflammation and recovery of tissue insulin sensitivity.

4. We have recently started looking at the microbiome on the mucosal surfaces, with special emphasis on the lung microbiome due to its perceived role in influencing the immune homeostasis at these surfaces. Morphine’s effects on the modulation of mucosal immune surveillance should correlate to the gross changes in the microbiome, which in turn, might have an effect on the general state of inflammation in the lungs. Our current studies have indicated that morphine does effect significant changes in the gut microbial composition. Future studies will look at the lung microbial changes in the infection and HIV models in the laboratory and its cross-talk/influence on the gut microbial population.

C. Peer-reviewed Publications

Santanu Banerjee, Jingjing Meng, Subhas Das, Anitha Krishnan, Justin Haworth, Richard Charboneau, Yan Zeng, Sundaram Ramakrishnan, Sabita Roy, Morphine induced sepsis is mediated by partial abrogation of endotoxin tolerance through modulation of miR-146a, Nature Scientific Reports, 3, 1977 (2013)


Santanu Banerjee, Anita Roy and Sampa Das; Binding of garlic (Allium sativum) leaf lectin to the gut receptors of homopteran pests is correlated to its insecticidal activity (2001), Plant Science, Volume 161, Issue 5, Pages 1025-1033.

D Patents


E Proceedings of Meetings

⇒ *Allium sativum* leaf lectin shows antifeedant properties towards homopteran insects, presented to the **Society of Biological Chemists**, New Delhi, India, 1999.

⇒ Efficiency of Mannose-binding plant lectins on controlling homopteran pests, presented to the **Society of Biological Chemists**, Bangalore, India, 2000.


⇒ Effects of PTH (1-34) on primary osteocytes, Accepted as a plenary poster in the 30th annual meeting of *The American Society of Bone and Mineral Research*, Hawaii, September 2007.

⇒ Morphine Modulation of IL17 Expression and Signaling in Bronchial Epithelial Cells, presented at the annual meeting of the *Society of Neuroimmune Pharmacology*, Clearwater, FL, USA, 2011.

⇒ Pathogens, TLRs, IL17 signaling and their crosstalk in bronchial mucosa, presented at the annual meeting of the *Society of Neuroimmune Pharmacology*, Honolulu, Hawaii, USA, 2012.

⇒ Talk entitled “Morphine attenuation of LPS tolerance- Role of miRNA” at the annual meeting of the *Society of Neuroimmune Pharmacology*, San Juan, PR, USA, 2013.

⇒ Morphine modulation of toll-like receptor and interleukin-17 receptor signaling in lung mucosa, presented at the bi-annual meeting of the *Society of Mucosal Immunology*, Vancouver, BC, Canada, 2013.

F. Research Support

Ongoing
1. NIH/NIDA; R01 to Prof. Sabita Roy; listed as key personnel.
Role of microRNAs in opioid drug abuse induced persistent inflammation and HIV disease progression
03/01/2011- 01/31/2016

Completed
1. Division of Basic and Translational Research, Univ of Minnesota intra-mural grant, Santanu Banerjee (PI)
A "humanized" mice model to delineate the mechanism of adipose tissue inflammation leading to insulin resistance in obesity and diabetes.
07/2012-06/2013

2. Department of Biotechnology, Government of India, Young Investigator grant award to Santanu Banerjee (PI),