Overview/Abstract

Inflammatory Bowel Disease (IBD) is a chronic condition characterized by recurring intestinal inflammation, which has been increasingly linked to neuroinflammatory responses and altered brain function. Recent evidence demonstrated that chronic intestinal inflammation suppresses brain activity by inducing neuroinflammation in mice, highlighting the critical yet understudied gut-brain connection in chronic inflammation. Emerging research suggests that this gut-brain interaction may contribute to neurological and psychiatric conditions, including major depression and Alzheimer's disease. Despite this growing evidence, the impact of targeting intestinal inflammation as a strategy to mitigate neuroinflammation remains unclear, limiting the development of effective therapeutic approaches that address both systemic and neurological complications of IBD.

This project aims to determine whether gut-targeted drug delivery strategies that reduce intestinal inflammation in IBD mouse models can also attenuate neuroinflammation. We hypothesize that effective treatment of intestinal inflammation will lead to reduced neuroinflammatory responses. By evaluating how intestinal-targeted therapies influence neuroinflammatory markers, this study will establish a mechanistic link between gut inflammation and brain health, providing essential preclinical data for future translational research. We will use a well-established mouse model of colitis to study intestinal inflammation and its associated neuroinflammatory effects. An optimized nanoparticle (NP)-based drug delivery system will be developed to improve anti-tumor necrosis factor-α (anti-TNF-α) therapy, a gold-standard treatment for IBD that remains limited by systemic side effects and rapid degradation before reaching the disease site. Our Specific Aims are:

Aim 1: To optimize the nanoformulation of anti-TNF NPs and validate their release profile and bioactivity. We will determine and optimize anti-TNF encapsulation efficiency and quantify release kinetics. Bioactivity will be assessed by ELISA, measuring anti-TNF-α both within the NPs and after release. In addition, functional effects will be evaluated using lipopolysaccharide-stimulated macrophage and microglia cell lines to determine how released anti-TNF-α modulates proinflammatory signaling, providing mechanistic insight that complements the quantitative data.

Aim 2: To evaluate the therapeutic efficacy of anti-TNF NPs in a colitis mouse model and determine how reduction of intestinal inflammation correlates with neuroinflammation modulation. We will first identify the optimal dosage and treatment regimen of anti-TNF-α NPs compared to anti-TNF-α alone in dextran sulfate sodium (DSS)-induced colitis. The therapeutic efficacy will be assessed by measuring both intestinal and neuroinflammatory responses using gene expression analysis and histology assessment. Neuroinflammation will be further evaluated using Positron Emission Tomography (PET) imaging and molecular analyses. Additionally, microbiota composition before and after treatment will be characterized to assess the impact of therapy on gut microbial changes. The correlation between reduced gut inflammation and neuroinflammatory markers will help define the extent to which gut-targeted therapy influences brain inflammation.

The impact of this study extends beyond establishing a mechanistic link between gut and brain inflammation. It will generate critical preclinical evidence examining the relationship between treating intestinal inflammation and its potential to improve neuroinflammation, addressing a major gap in understanding gut-brain interactions in chronic inflammatory diseases. The findings will lay the groundwork for future R21/R01 applications, expanding the investigation into human studies and clinical translation. If successful, this work could lead to novel therapeutic strategies targeting gut-brain inflammatory pathways for conditions such as IBD-associated neurological dysfunction and mood disorders, including IBD-related depression.