**Scientific Abstract**

Memory storage is a fundamental brain process essential for daily functioning, and its disruption is linked to various neurological disorders. Identifying the molecules involved in memory formation remains a complex challenge. EphrinB2 is a promising protein thought to be crucial for memory formation due to its involvement in several cellular processes that may be involved in this function. For instance, ephrinB2 is known to regulate glutamate transmission through the AMPA and NMDA receptors and to influence dendritic spine development. However, its specific roles in memory formation are not fully understood. This study thus aims to investigate the roles of ephrinB2 signaling in the formation of fear memory. Toward that end, we will employ behavioral, molecular, and cellular techniques, as well as advanced imaging approaches. Preliminary data indicate that deleting ephrinB2 in excitatory neurons or astrocytes within the basolateral amygdala (BLA) impairs long-term but not short-term fear conditioning memory. On the other hand, introducing ephrinB2 into the BLA has been found to increase cellular activity and enhance long-term memory formation for fear conditioning.

Based on previous studies and our preliminary findings, we propose that ephrinB2 plays a critical role in memory formation and enhancement within the BLA by modulating glutamate transmission, CREB activation, gene expression, and neuronal morphogenesis. We therefore plan to further elucidate how these molecular and cellular processes mediated by ephrinB2 in neurons and astrocytes are involved in the regulation of long-term memory formation in the BLA.

To explore this hypothesis, we have outlined four key research objectives: 1) Investigate how ephrinB2 regulates glutamate transmission during memory formation by controlling AMPA receptor trafficking, modulating NMDA receptors in excitatory neurons, and regulating glutamate reuptake through astrocytic transporters; 2) Explore how ephrinB2 influences gene expression changes in neurons and astrocytes following fear conditioning; 3) Assess the impact of ephrinB2 on the morphogenesis of neuronal spines following fear conditioning, both when acting directly in neurons and indirectly through astrocytes; and 4) Evaluate the effects of ephrinB2 in neurons and astrocytes on neuronal and astrocytic activity in the BLA during fear conditioning, as well as during short-term and long-term memory retrieval.

This research effort will provide critical insights into how ephrinB2 functions in neurons and astrocytes to support memory formation and clarify its role in neuron-astrocyte interactions during memory-related processes. Additionally, it will offer valuable information relevant to potential therapeutic approaches for managing fear-related and memory-related disorders through targeted modulation of ephrinB2 and its downstream effectors activities.