**Abstract**

Current treatments for Alzheimer's disease (AD) fail to arrest or reverse disease progression, highlighting the need for novel, efficacious therapies. Dysregulated microRNA (miRNA) expression has been increasingly established as a hallmark of AD, and these non-coding transcripts have been advanced as promising diagnostic biomarkers and/or therapeutic targets. To address the current lack of effective tools for the early detection and disease-modifying treatment of AD, the overarching aim of this study is to identify non-invasive biomarkers with the potential to aid in AD diagnosis and to guide disease-modifying treatment efforts. To that end, we will examine AD-associated patterns of miRNA dysregulation in male and female AD model rats and related regulatory mechanisms in the hippocampal-prefrontal cortex (HPC-PFC) pathway and in peripheral circulation. We will further examine promising novel therapies for AD including (i) the phytocannabinoid cannabidiol (CBD), with a particular focus on whether it can slow neurodegenerative processes through a bi-directional dialogue between miRNAs and the Wnt/β-catenin signaling pathway, and (ii) the targeting of specific miRNAs by silencing or activating them in the HPC-PFC. To achieve these experimental goals, we have formulated three specific aims:

In our **first Aim**, CBD will be administered in a streptozotocin (STZ)-induced rat model of sporadic AD, after which changes in cognitive and emotional function will be correlated with shifts in the expression of miRNAs in the HPC-PFC pathway, with an additional focus on targets related to inflammation, CBD signaling, AD pathology, and β-catenin. We will also investigate peripheral miRNAs as potential biomarkers of AD progression and treatment response. These findings will reveal significant AD-related genetic changes that can be blocked by CBD treatment and highlight the potential value of peripheral miRNAs as biomarkers of AD.

In our **second Aim**

In our **third Aim,** we will explore whether specific miRNAs mediate AD-related cognitive and emotional dysfunction and the therapeutic effects of CBD by using agomir and antagomir constructs to activate or inhibit specific miRNAs. The association between changes in miRNA expression, cognitive/emotional pathology, inflammatory markers, CBD targets, AD pathology-related targets, and β-catenin will then be further assessed.

We anticipate that the **successful completion of these experiments** will (i) clarify whether β-catenin is a key mediator of the therapeutic-like effects of CBD, (ii) highlight the potential therapeutic impact of activating or inhibiting specific miRNAs as an approach to overcoming emotional and memory deficits in AD, and (iii) define the importance of miRNAs as mediators of the neuroprotective benefits of CBD in both male and female AD model rats, providing a new foundation for the treatment of this and related neurodegenerative diseases. Ultimately, the establishment of a validated noninvasive biomarker of AD or associated therapeutic targets will guide the future development of early diagnostic tools, preventative and remedial strategies, and effective pharmacological treatments for dementia.