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Scientific abstract – *Examination of the therapeutic effects of cannabidiol (CBD) on Alzheimer’s disease-related cognitive and emotional dysfunction in male and female rats*

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 aims of this study are to explore whether AD-related pathology can be prevented or reversed by cannabidiol (CBD) and to identify noninvasive biomarkers with the potential to aid the diagnosis and disease-modifying treatment of AD patients. CBD has a therapeutic potential as a treatment for several neuropsychiatric and neurodegenerative disorders, however, the mechanisms through which CBD impacts AD pathogenesis are not entirely clear. 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 hippocampal-PFC pathway, with an additional focus on targets related to inflammation, CBD signaling, AD pathology, and the Wnt/β-catenin pathway. 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**, we will determine whether CBD can protect against AD phenotypes through β-catenin-mediated mechanisms. CBD enhances Wnt/β-catenin pathway activity to exert neuroprotective activity against Aβ-induced neurotoxicity in AD. If we find that the downregulation of β-catenin in the PFC/hippocampus blocks the preventative effects of CBD on AD-related pathology, this would suggest that β-catenin is a key mediator of the therapeutic effects of CBD. In our **third Aim,** we will explore whether specific miRNAs mediate AD-related cognitive and emotional dysfunction and contribute to the therapeutic effects of CBD by using agomir and antimir constructs to activate or inhibit specific miRNAs.

We anticipate that the successful completion of these experimentswill (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.