**Noncoding RNAs in Alzheimer's Disease and Related Dementias (R21)**

Irit Akirav

Progressive impairment of memory and cognition is a key clinical feature of **Alzheimer’s disease** **(AD)**, which is characterized by extracellular **amyloid β-protein (Aβ)** deposits in the brain (plaques), intraneuronal tau pathology, neuronal cell death, vascular dysfunction, and inflammation that ultimately manifest in the form of debilitating neuropsychiatric symptoms. No effective cure for AD has been established to date, underscoring the need to identify novel effective compounds that can counteract the AD course.re that modulate gene expression and are closely linked to s Exposing hippocampal and cortical neurons to **Aβ peptide** activates glycogen synthase kinase 3β (GSK-3β) and thereby drives *Wnt/β-catenin signaling pathway* degradation, contributing to neurofibrillary tangle formation and impaired neuronal survival. Moreover, β-catenin binds to the Dicer1 gene encoding the Dicer protein, which is involved in the cleaving and formation of all **miRNAs**. As such, miRNAs are modified as a function of AD whereupon they can regulate genes involved in the Wnt signaling pathway. **Cannabidiol (CBD)** is a safe, non-psychoactive phytocannabinoid that reportedly exhibits immunomodulatory activity in neurodegenerative disease, ameliorating the symptoms of AD and retarding cognitive decline. CBD inhibits GSK-3b phosphorylation and thereby enhances **Wnt/β-catenin** signaling, suggesting that CBD may exert neuroprotective effects by rescuing the Wnt/β-catenin pathway and consequently impacting the expression of miRNAs.

In our planned study, we propose to conduct two major behavioral and molecular experiments to examine the expression of several miRNAs associated with AD and related regulatory mechanisms to provide novel therapies against AD. In our **first experiment**, CBD will be administered in a streptozotocin (STZ)-induced rat model of AD, after which correlations between behavior cognitive and emotional function will be correlated with alterations in the expression of **miRNAs in the prefrontal-hippocampal circuit**, as well as targets related to inflammation, CBD signaling, AD pathology, and β-catenin. We will also investigate **peripheral miRNAs and inflammatory cytokines as potential biomarkers** of AD and treatment response. These findings will reveal significant AD-related genetic changes that can be reversed by CBD treatment and highlight the potential value of peripheral microRNAs as biomarkers of AD. In our **second experiment**, we will explore whether different miRNAs are critically involved in AD-related cognitive and emotional dysfunction and the therapeutic effects of CBD by using agomirs and antagomirs to inhibit/activate specific miRNAs in the PFC-hippocampal pathway in CBD-treated AD model animals, after which the relationship between changes in miRNA expression, cognitive/emotional pathology, inflammatory markers, CBD targets, AD pathology-related targets, and β-catenin will be assessed. Together, these experiments may aid in defining the therapeutic role of CBD in the treatment of AD through miRNA-regulated and suggest how CBD may slow neurodegenerative processes. Ultimately, the establishment of a validated noninvasive biomarker of AD or associated targets will guide the future development of early diagnostic tools, preventive strategies, and effective pharmacological treatments for dementia.