

RT-QuIC and FRET assay, we expect EVs isolated from DLB patient samples to support seeded aggregation, whereas EVs from AD and HC will not. **DISCUSSION/SIGNIFICANCE:** To date, no diagnostic or less invasive biomarkers can distinguish DLB from AD. The successful completion of the aims outlined in this proposal will identify characteristics of bpEVs that differentiate DLB from AD or HC and support the development of bpEVs as a non-invasive, early biomarker to diagnose patients presenting with dementia from DLB.

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Epicardial adipose tissue and cardiometabolic health in youth-onset type 2 diabetes undergoing vertical sleeve gastrectomy

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OBJECTIVES/GOALS: The goal of this study is to investigate the potential independent relationship between epicardial adipose tissue (EAT) and cardiometabolic health in youth-onset type 2 diabetes (T2D) and explore changes in EAT as a potential mediator of changes in cardiometabolic health in response to vertical sleeve gastrectomy (VSG). **METHODS/STUDY POPULATION:** We will assess glycemic control, insulin sensitivity and secretion in youth with T2D before and 3 months after VSG. Fasting labs, anthropometrics, and a 4-hour, frequently sampled liquid mixed meal tolerance test (45g carbohydrates, 14g fat, and 14g protein) were performed. Calculations included glucose, insulin, and GLP-1 area under the curve (AUC), Matsuda Index, HOMA-IR, and oral disposition index (DI). These cardiometabolic outcomes will then be assessed for associations between total EAT volume, measured from cardiac MRI. **RESULTS/ANTICIPATED RESULTS:** Previous studies have shown that individuals with obesity have higher EAT than lean controls, and adults with T2D have even higher EAT than obese controls. Therefore, we anticipate that our participants will have higher volume of EAT than what has been reported in the literature and that they will have worsening cardiometabolic outcomes without MBS. Our anticipated results will include: Weight and BMI, hemoglobin A1c, diabetes medications, Matsuda Index, HOMA-IR, DI, and glucose and insulin AUC during an MMTT. Cardiac MRI's are being analyzed and will give total EAT volume and will be analyzed for correlations with the cardiometabolic outcomes of body composition, aortic stiffness, blood pressure, cardiac structure and function, as well as lipid panel and insulin sensitivity. **DISCUSSION/SIGNIFICANCE:** This study is the first to specifically assess EAT in adolescents with T2D. The assessment of EAT will be done with gold-standard MRI and correlated with cardiometabolic health assessed by gold-standard methods. Together, the results will give insight into EAT as a potential independent cardiometabolic risk factor in adolescents undergoing VSG.

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Fractalkine isoforms using gene therapy differentially regulate microglia activation and vascular damage in the diabetic retina

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OBJECTIVES/GOALS: Retinal inflammation caused by the activation of resident macrophages (microglia) during diabetes exacerbates glial cell dysfunction, resulting in neuronal loss. The goal is to use rAAV gene therapy to deliver neuronal-derived fractalkine (FKN), minimizing inflammation and vascular damage in the diabetic retina. **METHODS/STUDY POPULATION:** The human microglial receptor (CX3CR1) binds to FKN, a protein that is expressed on neuronal membranes (mFKN), and undergoes constitutive cleavage to release a soluble domain (sFKN). Deficiencies in CX3CR1 or FKN showed increased microglial activation and elevated retinal pathology. To understand the mechanism by which mFKN and sFKN regulate microglia function, recombinant adeno-associated viruses (rAAVs) expressing mFKN or sFKN were delivered to intact retinas during diabetes. Markers of neuronal loss, vascular damage, and inflammation were analyzed. We hypothesize that the administration of rAAV-sFKN but not rAAV-mFKN will prevent vascular and neuronal damage, and improve visual function. **RESULTS/ANTICIPATED RESULTS:** rAAV-sFKN minimized microglial activation, blood vessel rupture, fibrinogen deposition, and prevented neuronal loss, compared to mice treated with rAAV-mFKN in a mouse model of diabetic retinopathy (DR). rAAV-sFKN treated mice showed improved visual acuity using a two-choice discrimination task through learning-based behavior. rAAV-sFKN treatment correlated with the success rate of the mice finding the reward based on their ability to distinguish visual cues. Future studies will test the effects of rAAV-sFKN and rAAV-mFKN on microglia inflammatory cytokine release, optic nerve damage and synaptic neurotransmission, peripheral immune responses, and transcriptomic changes in microglia during diabetes. **DISCUSSION/SIGNIFICANCE:** Current therapies for DR are ineffective in restoring vision. rAAVs-sFKN delivery appears to act as a neuroprotective approach in the diabetic retina. sFKN serves as an alternative pathway to implement translational and therapeutic approaches, minimizing pathology and improving visual function.

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HMGB1 Localization as a Driver of Carcinogenesis in RDEB-Associated Squamous Cell Carcinoma

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OBJECTIVES/GOALS: This study investigates whether localization of high mobility group box 1 (HMGB1) controls inflammatory signaling and DNA damage response in human keratinocytes, the cell of origin for squamous cell carcinoma (SCC). SCC is especially