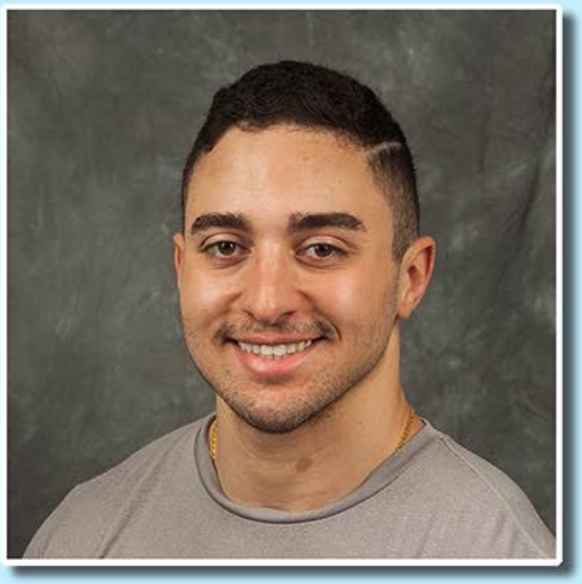

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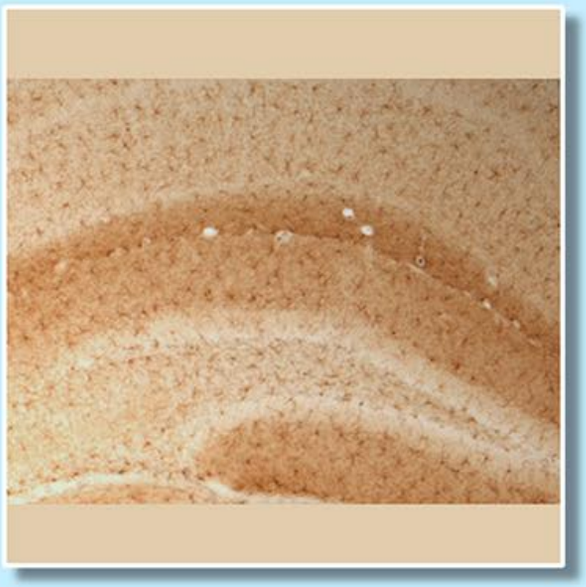

Section of a mouse hippocampus

Development of a New Transgenic Alzheimer's Disease Mouse Model to Evaluate Therapeutic Approaches using Adeno-Associated Virus (AAV)

Alzheimer's disease (AD) pathology involves the accumulation of amyloid-β (Aβ) and hyperphosphorylated tau deposits in brain tissue leading to degradation of cortical brain regions such as the hippocampus. It is hypothesized that an imbalance between the production and clearance of tau and Aβ leads to plaque accumulation and neuronal cell death. Clearance is achieved via glymphatic circulation which uses paravascular pathways engaging in the exchange/flow of water and soluble proteins between cerebrospinal (CSF) and interstitial fluids (ISF). This ISF bulk flow is facilitated by a specific water channel protein termed aquaporin 4 (Aqp4), and it is believed that diminished ISF bulk flow leads to accumulation of tau and Aβ. Aqp4 knockout mice (KO) exhibit reduced interstitial clearance of fluorescent tracers and Adeno-Associated virus (AAV) from the brain. Here, a new mouse model was generated utilizing strategy crosses between an Alzheimer's mouse model (3xTg-AD) with an Aqp4 KO mouse predicting that this new model would show an accelerated AD phenotype characterized by increased tau and Aβ deposits in mouse cortical regions. In parallel, gene therapy using an AAV9-GFAP-Aqp4 construct was used to evaluate the therapeutic efficacy of Aqp4 expression on tau levels. The double transgenic mouse (3xTg-AD;Aqp4 KO) was phenotyped and characterized via western blot, and behavioral testing. We observed that the 3xTg-AD;Aqp4 KO mice exhibit significantly more tau protein levels in the hippocampus compared to whole brain. Also, double transgenic mice treated with a AAV9-GFAP-Aqp4 construct showed a reduction of tau specifically in the hippocampus. Further characterization using immunohistochemistry is necessary to fully understand the pathology of this new (3xTg-AD;Aqp4 KO) mouse model. These findings provide evidence that clearance of interstitial fluid/metabolic waste including protein deposits is impacted by aquaporin 4 water channels expressed in astrocytes. This may have implications on future Alzheimer's therapies which utilize AAV vectors for novel gene therapies which reduce protein deposits characteristic of Alzheimer's disease.