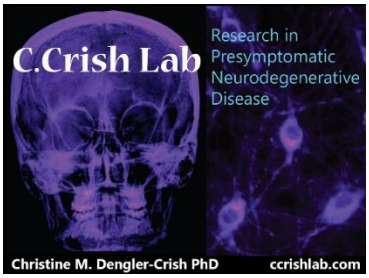

The methodology presented in **SFN 2019 poster #564.15** directly aligns with work currently being conducted by Kent State University Biomedical Graduate Program doctoral student **Gabrielle Frame** in the Christine Crish Lab at the Northeast Ohio Medical University.

Gabbie recently received a *Young Investigator Student Fellowship Award for Female Scholars in Vision Research* from **Prevent Blindness Ohio** to work on the following project:

Investigating the neuroprotective effects of fingolimod on visual system deficits in Alzheimer's disease

Summary

Alzheimer's disease (AD) is a neurodegenerative disorder that is mainly characterized by deficits in cognition and memory. However, some of the earliest symptoms, which can occur years before the onset of cognitive decline, affect the visual system. Patients with AD often report decreased visual acuity and decreased contrast sensitivity. Historically, these deficits have been attributed to pathology in the visual cortex. However, retinal structural changes and neurodegenerative events seen in other diseases of the visual system, including ocular inflammation and retinal ganglion cell (RGC) loss, have been identified in AD. Furthermore, AD is differentiated from other dementias by the presence of extracellular aggregations of amyloid beta and intracellular neurofibrillary tangles composed of hyperphosphorylated tau, both of which have been identified in several layers of the retina in AD. While AD pathology in the visual system is evident, treatments targeting potential mechanism(s) underlying vision loss have not been explored. Improvement and/or prevention of visual dysfunction is a key factor in improving quality of life in the aging population.

One such way to prevent vision loss in AD may be through the use of anti-inflammatory drugs. Fingolimod, an immune modulating drug, is currently FDA-approved for the treatment of multiple sclerosis, which causes increased levels of inflammation in the nervous system. Fingolimod is also a protein phosphatase 2A (PP2A) activator. PP2A is responsible for the regulation of many targets, including tau, a main protein involved in neuronal cytoskeleton stabilization and one of the major misfolded proteins in AD pathology. Based on these two properties, fingolimod is a promising candidate for improving visual system deficits that occur with neurodegeneration. Fingolimod has also shown to reduce tau and amyloid pathologies in other AD mouse models.

This proposal will use 3xtg, a well-characterized AD mouse model that exhibits both amyloid and tau pathology, along with age- and sex-matched control C57BL6J mice. Beginning at 3 months of age, which is considered pre-pathological in 3xtg mice, half of the animals will be administered fingolimod in their drinking water, while the other half receives untreated water. Throughout the study, animals will undergo optomotor response testing, which allows for measurement of visual acuity based on reflexive movement of the head when moving stimuli are presented. Pattern electroretinogram (PERG) measurements will be collected to determine the function of RGCs. In-vivo retinal imaging will be used to track AD pathology in the retina over time and in response to treatment. Two days prior to sacrifice, animals will receive intravitreal injections of cholera toxin subunit b, a neuronal tract tracer, to assess axonal transport, a key event necessary for neuronal function and survival. Finally, multichannel immunofluorescence will be used to analyze RGC density and loss, inflammation, and AD pathological proteins- tau and amyloid, in retinas and brain sections taken through the visual brain targets.

These experiments will be the first to test the therapeutic potential of fingolimod to reduce and/or prevent AD pathology in the visual system and preserve vision. Based on previous studies and preliminary data from our lab, I anticipate that fingolimod treated animals will exhibit increased visual acuity compared to untreated controls. Through the use of PERG, RGC function will be measured in-vivo, and, to our knowledge, will be the first such characterization of this strain. Further, I expect that AD pathology, including amyloid plaques, tau, and inflammation will be reduced in the fingolimod-treated 3xtg mice.

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