Alzheimer's disease (AD) is the most prevalent neurodegenerative disease of aging, characterized by the accumulation of Aβ plaques and neurofibrillary tangles (NFT) consisting of tau protein, coupled with neuroinflammation and cognitive decline. While much of the research in AD initially focused on targeting plaques and tangles in the brain, in recent years research has expanded to include consideration of the role of neuroinflammation. However, the role played by the immune system in AD pathogenesis is not limited to the brain. Recent studies suggest a critical, but to date underappreciated, role for systemic immune signaling originating in the periphery in disease progression. These include the release of inflammatory factors that can promote both migration of peripheral immune cells to the brain as well as disruption of the blood-brain barrier (BBB), leading to the entry of peripheral immune cells which can contribute to ongoing neurodegeneration. What drives these changes in the peripheral immune system?

Results from several studies increasingly suggest a role for age-dependent alterations in the gut microbiome, called dysbiosis, and the gut's increased susceptibility to infection. We propose that these alterations can impact microbial metabolites, such as short chain fatty acids (SCFAs), and lead to perturbations in the intestinal immune system with effects on gut integrity and inflammation. Thus, through this means, gut microbial dysbiosis can result in the increased systemic release of pro-inflammatory factors, including microbial danger signals, which can on their own drive further neuroinflammation as well as prime immune cells for entry into the brain. The natural metabolite gut urolithin A (UA) has recently been reported to be neuroprotective in proteotoxic models of Alzheimer's disease, including our own new preliminary data showing improvement in cognitive function and reductions in insoluble cortical $Aß_{42}$ levels and hippocampal CA1 inclusions in the 3xAD mouse model following oral UA administration. This model expresses human genes for APP, PSEN1, and tau resulting in a progressive age-related presentation of Aβ and tau deposits and neuroinflammation. UA's neuroprotective effects could be mechanistically linked to improved cognitive outcomes through multiple mechanisms. First, it is possible that UA has direct neuroprotective effects in vulnerable hippocampal and cortical populations in the CNS. It is also however and perhaps equally possible that effects of UA may be indirect due to the compound's known ability to reduce both losses in gut integrity and increased inflammation[3,4] that may arise from elevations in pro-inflammatory bacteria and cell signatures which are observed in AD patients and in various mouse models, including, as recently shown by our laboratory, in the 3xAD mice. Interestingly, it is possible that UA could be mediating these effects in part through boosting autophagy in the gut as well. Indeed, it has been shown that diseases linked to reduced autophagy like inflammatory bowel disease are major risk factors for T cell mediated intestinal inflammation, dysbiosis, as well as AD predisposition.

In this project, we propose to directly interrogate the contribution of age-related gut dysbiosis and susceptibility to infection to neurodegenerative phenotypes associated with the 3xAD mouse model. Specifically, we will determine: (1) whether changes in the gut microbiome or pro-inflammatory gut infection altering gut immune function impact on age-related cognitive and neuropathological effects and (2) whether the neuroprotective effects of UA involve restoration of gut health in this mouse model.

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