‘CJDSGN Memorial Award 2019 in memory of Michael John Dempsey’- $25600 – awarded in October 2019

‘The role of co-pathologies in the clinical presentation of prion disease’ covering Year 1 (Aim 1 $12,000 and Aim 2 $13,600)

A unique feature of prion diseases is their range of clinical presentations which affect memory and movement. While these features can be attributed to differences in the shape of the misfolded prion protein, we do not understand how or why prions with different shapes (prion strains) have different clinical presentations. Another recent observation is the presence of co-pathologies, or misfolded proteins associated with other neurodegenerative disorders that have either the clinical presentation of deteriorating movement (alpha-synuclein in Parkinson’s disease and TDP-43 in Motor Neuron Disease) or deteriorating memory (Amyloid-beta and Tau in Alzheimer’s disease). We propose that some of the clinical variation in prion disease is due to these co-pathologies and that the presence of co-pathologies is dependent on the shape (or strain) of the misfolded prion protein. We will use our unique panel of mouse adapted human prion strains to investigate this proposal.

Aim 1: Characterize the memory and movement phenotype of mice infected with these three prion strains.

- Analyze the gait of mice with clinical prion disease
- Analyze the memory of mice with clinical prion disease

Aim 2: Characterize the co-pathologies present in the brains of mice infected with these three prion strains

- Perform immunohistochemistry and western immunoblot analysis of tissue derived from mice with clinical prion disease to determine whether the amount, form, location or conformation of proteins such as alpha-synuclein, tau, TDP-43 and Amyloid-beta are altered in prion disease and if that alteration is associated with a specific strain of prion disease.

Ms Asmaa Hussein was recruited to initiate this project in early 2020. To date progress has been made to characterize the lesion profiles and PrPSc deposition patterns in three different prion strains. These profiles will be correlated with data collected on gait abnormalities. Due to COVID-19 restrictions we have been unable to perform memory analysis experiments which would have involved commencing in vivo experiments. However, we have instead used existing tissue to correlate lesion profiles with markers of inflammation. We have also performed western immunoblot and immunohistochemical analysis for the presence of co-pathologies and are the in the process of analyzing this data to determine whether prion strain correlates with the presence of specific copathlogies.