September 11, 2017: Dr. Brian Kraemer, PhD, Research Associate Professor, Gerontology & Geriatric Medicine, UW, Investigator, VA Puget Sound Health Care System/ ADRC Affiliate Member - *MSUT2: a novel therapeutic target for Alzheimer's Disease*

Dr. Brian Kraemer's talk focused on his group's work to understand the molecular mechanisms involved in the protein pathologies that lead to symptoms of Alzheimer's disease, frontotemporal lobar degeneration (FTLD), and/or amyotrophic lateral sclerosis (ALS). To study the role of the tau protein in Alzheimer's disease, they are using the *c. elegans* worm and the mouse as models of tau toxicity and platforms to discover genes that control tau toxicity.

Specifically, Kraemer's group expose worms to chemical mutagens to mutate genes, and then they look for tau models that, despite the tau mutation, can move normally. Doing so, they found that the gene sut- 2/MSUT2 appears to be a potential new modulator of tau toxicity. This gene, present across all species, plays a role in shuttling proteins in the cytoplasm. In humans, sut- 2/MSUT2 is expressed in the hippocampus neurons; in worms, this gene's expression is located in the motor neurons. Using CRISPR, they entirely eliminated or overexpressed MSUT2 and observed near complete suppression of tau. They conclude that sut- 2/MSUT2 loss of function is protective.

Kraemer presented an overview of the results of loss of function of sut- 2/MSUT2 in both *c. elegans* and mouse models of tau pathology. In *c. elegans*, loss of msut2 ameliorates the behavioral phenotype, tau aggregation, and neurodegeneration, and the loss of function model has no obvious phenotype or lifespan changes. Conversely, over-expression worsens the behavioral phenotype, increases tau aggregation and neurodegeneration. Likewise, in a mouse model, the loss of msut2 decreases pTau, aggregation, neuron loss, and inflammation. With sut- 2/MSUT2 over-expression, they see more pTau, abundant pre tangle tau, which drives neuron loss and inflammation.

In terms of molecular mechanisms, the questions remains: How does sut- 2/MSUT2 modulate tau pathology? The first clue is that sut- 2/MSUT2 and the PABPN1 gene are partners—responsible for 3 prime processing where the poly(A) tail is cleaved and extended. PABPN1 works as the ruler that measures poly(A) tail length and ensures the proper length of every RNA messenger made. Interestingly, expansions in PABPN1 cause oculopharyngeal muscular dystrophy (OPMD), a rare genetic muscle disorder with

onset during adulthood most often between 40 and 60 years of age. Some of the patients carrying two copies have dementia. Kraemer thinks that the loss of PABPN1 leads to shorter poly(A) tails, which worsens tau aggregation. In contrast, the loss of sut-2/MSUT2 function can ameliorate tauopathy by shifting he balance of control of polyadenylation, in that loss of sut- 2/MSUT2 leads to a longer poly(A) tail, which protects against tau aggregation.

In the discussion, the group discussed the possibilities of understanding the 2/MSUT2 genetics of their patients with tau-based neurodegenerative diseases. They pointed to one of Tom Bird's patients, a man recently profiled in the *New York Times*, who has surpassed the expected age-of-onset of dementia due to an inherited tau mutation. One intriguing possibility is that this patient also carries a tau suppressor gene that is counteracting the pathogenic tau mutation.

Kraemer's group will now extend the research demonstrating that sut- 2/MSUT2 controls tau aggregation and toxicity in *c. elegans* worm and human cell models, and therefore determines a cell's vulnerability to tau pathology. The team aims to understand how sut-2/MSUT2 influences tau pathology in living organisms at a deeper level of biological detail. Specifically, how are sut- 2/MSUT2 and PABPN1 influencing the polyadenylation machinery and tau aggregation? They will now try to address mechanistic hypotheses with a no-holds-bar screening approach and tools to manipulate polyadenylation to explore the effects on tau aggregation. This knowledge may provide a novel candidate therapeutic target for pharmacological intervention, a key goal of the UW ADRC.