Alzheimer disease and other tauopathies likely result from a combination of genetic, life history, and endogenous and environmental exposures which contribute to the risk of developing clinically apparent disease during an individual's lifespan. While significant progress has been made in the identification of genetic contributors which can predispose to early onset tauopathies, as well as some of the life history co-morbidities which can influence age of onset of clinically apparent disease, there has been limited insight into the endogenous and environmental exposures, collectively referred to as the exposome, which likely impacts the risk of the development of tauopathies. In particular, the role of manmade chemicals in the development of neurodegenerative disease has been highlighted by several instances of acute onset neurodegenerative disease associated with specific, often high level, chemical exposures. The role of ongoing exposure to the diverse, largely untested, set of the estimated over 100 thousand manmade chemicals currently in use, in the development of neurologic disorders is less clear.

One key issue in assessing the potential hazard of specific chemicals or chemical mixtures in impacting the pathophysiology of neurodegenerative disorders, including tauopathies, is the availability of mechanistically linked assays, which can assess key molecular initiating events, in development of neurologic disease. While there are ongoing and important efforts to develop mid to high throughput assays to assess neurodevelopmental toxicity, particularly using the zebrafish as a vertebrate model, there is a glaring lack of mid to high throughput assays to assess the effects of chemical exposure on key molecular events, such as the formation of neurofibrillary tangles and plaques, in the development of neurodegeneration associated outcomes. In this project, we will take advantage of existing validated live brain slice assays from the transgenic mice expressing *MAPT* encoding the P301L/S320F double mutation to quantitatively assess the formation of neurofibrillary tangles in response to exogenous agents. The Lewis laboratory (Dr. Jada Lewis, MBI) have already demonstrated its capability as a screening assay to identify potential therapeutic agents which can modulate the development of this key event in the development of tauopathies. In collaboration with the Lewis laboratory we will adapt this existing validated assay to assess the potential of selected high production volume manmade chemicals at environmentally relevant concentrations to impact the formation of neurofibrillary tangles in this model system. We will focus our initial efforts on limited set of eighteen high risk high exposure chemicals for which there already exists significant concern about their potential neurotoxicity. This work, if successful, will develop a foundation for further targeted screening of environmental chemicals of concern and will fill an important gap in our capability to assess and understanding of the role of environmental chemicals in the development of tauopathies.

FVSP student role: The student would work with a post-doctoral fellow and a scientist on the project. The student would work on testing a specific limited set of chemicals or exogenous stressors to assess Tau formation in the brain slice assay. Specific activities include long term organotypic brain slice culture from both WT and Tau mutant mouse, chemical treatments, AAV transfection with TAU reporter, and imaging of the samples, and data analysis.

Reference:

Croft, C.L., Goodwin, M.S., Ryu, D.H. *et al.* Photodynamic studies reveal rapid formation and appreciable turnover of tau inclusions. *Acta Neuropathol* **141**, 359–381 (2021). https://doi.org/10.1007/s00401-021-02264-9