# The use of *Drosophila melanogaster* to study the interactions between sleep and neurodegenerative diseases for pre-clinical testing

Dr Jason R. Gerstner, PhD, Elson S. Floyd College of Medicine, Steve Gleason Institute for Neuroscience, Washington State University, Spokane WA, USA

## Abstract

Statement of the Problem: Neurodegenerative diseases, including Alzheimer's (AD) and Parkinson's, affect millions of people across the world, and include a broad range of conditions from the progressive loss of nerve cells. New intervention opportunities and discovery of novel compounds to treat neurodegenerative disease are often slowed in pre-clinical testing stages, particularly in mammalian models of aging-related disease, such as AD, can take months to years to test. Disruption of sleep behavior may not only represent a clinical manifestation of neurodegenerative disease but may be a contributing factor to disease onset and progression. Here we describe the use of the fruit fly, *Drosophila melanogaster*, for pre-clinical screening of compounds and targeted proteins using behavioral measures such as sleep. Methodology: Transgenic flies which contain genetic manipulations associated with neurodegenerative disease are assayed using the either a video tracking system or the Drosophila Activity Monitoring System (DAMS). DAMS measures activity by counting beam breaks over 5 minute bins and averaged over 60 minutes to obtain sleep/wake behavior, with a minimum bout of sleep defined by 5 minute period of inactivity. Findings: AD model flies which express the human Aβ42 transgene in neurons show fragmented sleep that is rescued by overexpression of fatty-acid binding proteins, or treatment with Glitazone drugs. Glitazone treatment in a fly model of Gaucher's/Parkinson's (GP) disease also rescues sleep deficits, as well as climbing defects. Glitazone treatment restored normal protein levels of Ref(2)P, a marker of autophagic flux, in GP flies. Conclusion & Significance: *Drosophila* sleep behavior may serve as a rapid pre-clinical screening tool for assaying potential therapeutic compounds or relevant proteins for the treatment of neurodegenerative disease. Strategies targeting the relationship between fatty-acid binding protein signaling and autophagy cascades may represent a novel pathway for treatment across multiple neurodegenerative diseases or related proteinopathy.

## Publications

1. Needham H, Torpey G, Flores CC, Davis CJ, Vanderheyden WM, Gerstner JR. (2022) A Dichotomous Role for FABP7 in Sleep and Alzheimer's Disease Pathogenesis: A Hypothesis. Front Neurosci. Jun 30;16:798994. doi: 10.3389/fnins.2022.798994.
2. Shola-Dare O, Bailess S, Flores CC, Vanderheyden WM, Gerstner JR. (2021) Glitazone Treatment Rescues Phenotypic Deficits in a Fly Model of Gaucher/Parkinson's Disease. Int J Mol Sci. Nov 25;22(23). doi: 10.3390/ijms222312740.
3. Vanderheyden WM, Lim MM, Musiek ES, Gerstner JR. (2018) Alzheimer's Disease and Sleep-Wake Disturbances: Amyloid, Astrocytes, and Animal Models. J Neurosci. Mar 21;38(12):2901-2910. doi: 10.1523/JNEUROSCI.1135-17.2017.
4. Gerstner JR, Lenz O, Vanderheyden WM, Chan MT, Pfeiffenberger C, Pack AI. (2017) Amyloid-β induces sleep fragmentation that is rescued by fatty acid binding proteins in Drosophila. J Neurosci Res.95(8):1548-1564. doi: 10.1002/jnr.23778.
5. Lim MM, Gerstner JR, Holtzman DM. (2014) The sleep-wake cycle and Alzheimer's disease: what do we know?. Neurodegener Dis Manag. 4(5):351-62. doi: 10.2217/nmt.14.33.

**Photograph**



## Biography

Dr Jason R. Gerstner is an Assistant Professor in the Department of Translational Medicine and Physiology at the Elson S. Floyd College of Medicine at Washington State University in Spokane, WA USA. He is also the inaugural Steve Gleason Institute for Neuroscience Fellow and a core faculty member of the Sleep and Performance Research Center. Dr. Gerstner has expertise in the neuroscience of sleep and circadian rhythms with a specialty focus on glial cells, particularly astrocytes. His research interests are broad, and his laboratory uses multiple species and transgenic approaches to test how underlying cellular, molecular and genetic regulation of sleep and circadian rhythms interact with other processes, such as memory formation and neurodegenerative disease progression.

Email: j.gerstner@wsu.edu

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