We ask fundamental questions in the biology of aging, with a particular focus on how the brain modulates longevity and health. Using the fruit fly *Drosophila melanogaster*, we study the cells and molecular pathways that maintain the healthy state of animals throughout their life course, and how these biological processes are influenced by environmental conditions and social opportunities. Our work aims to provide conceptual and mechanistic insights into contemporary challenges to human health.

The Lyu laboratory is built to rigorously investigate a set of biomedical traits that incorporates an understanding of aging, neurobiology, molecular genetics, and systems biology. We believe invertebrate models, such as *Drosophila*, offer a unique opportunity to understand the complex processes behind aging, to discover novel mechanisms for translational application, and to equip next-generation scientists with interdisciplinary perspectives and skills. Our team welcomes everyone who appreciates scientific curiosity, intellectual diversity, and inclusion.

The current research in our laboratory follows three interconnected aspects of aging:

**Brain-Body Communications**

It has been known for decades that the brain processes and integrates extrinsic inputs to elicit neuronal and behavioral changes. However, little is known about the health outcomes of these brain activities. We have recently discovered that behavior, metabolism, and lifespan in *Drosophila* are affected by whether flies are provided a choice of different nutrients or a single, complete medium (Ro *et al*. 2016). Multiple lines of evidence strongly suggest that a serotonin dependent motivation or reward for sugar feeding (i.e., a sugar ‘craving’), rather than its consumption, may be the cause for changes in lifespan (Lyu *et al*. 2021a). Manipulating a specific serotonin receptor is sufficient to change lifespan and metabolic health, likely through instructing the body to process nutrients in different ways (Lyu *et al*. 2021a). This portion of our research is powered by combining cutting-edge techniques including optogenetics, metabolomics, and computational modeling to understand how crosstalk between neurons and peripheral cells influences longevity.

Yang Lyu, Kristina J. Weaver, Humza A. Shaukat, Marta L. Plumoff, Maria Tjilos, Daniel E.L. Promislow, Scott D. Pletcher. (2021a) *Drosophila* serotonin 2A receptor signaling coordinates central metabolic processes to modulate aging in response to nutrient choice. eLife. 10: e59399.

(Featured by eLife insight - Aging and Diet: To choose or not to choose)

Jennifer Ro, Gloria Pak, Paige A. Malec, Yang Lyu, David B. Allison, Robert T. Kennedy, Scott D. Pletcher. (2016) Serotonin signaling mediates protein valuation and aging. eLife. 5:e16843.

**Homeostatic Control and Network Biology**

Aging arises from complex interactions among multiple biochemical products. Instead of thinking of each molecule acting in isolation, we realized that the homeostatic states of cells are determined by the collection of the whole (i.e. biological networks, Hoffman *et al*. 2017). Using genetic perturbations and systems biology approaches, our work has found links between network integrity, physiological robustness, and mortality (Lyu *et al*. 2021b). We are currently seeking to understand how network structures and highly connected “hub” molecules together shape the healthy states of animals.

Yang Lyu\*, Daniel E.L. Promislow, Scott D. Pletcher\*. (2021b) Serotonin signaling modulates aging-associated metabolic network integrity in response to nutrient choice in *Drosophila melanogaster*. Communications Biology. 4 (1), 1-13. (\*co-corresponding authors)

Jessica M. Hoffman\*, Yang Lyu\*, Scott D. Pletcher, Daniel E.L. Promislow. (2017) Proteomics and metabolomics in aging research: From biomarkers to systems biology. Essays in Biochemistry. 61 (3), 379-388. (\*These authors contributed equally to this work)

**Neurodegeneration**

Does the brain regulate how it ages? Maybe. We think the answer could be found in glia, the non-neuronal cells in the nervous system, whose main function is to nourish, support, and protect neurons. We are interested in how these cells respond to environmental stress, and hypothesize that the failure of intrinsic protective mechanisms leads to the onset and progression of neurodegeneration. This branch of our research will build disease models to investigate environmental triggers and genetic components of neurodegenerative disorders, with a particular interest in defining the molecular nature of the diseased state of the brain.