

March 6, 2017: Daniel Promislow, Professor, Departments of Pathology and Biology, University of Washington/ ADRC Affiliate Member - *Systems biology of neurodegenerative disease in the fruit fly, Drosophila melanogaster*

In recent years, numerous laboratories have developed the fruit fly, *Drosophila melanogaster*, as a powerful model to study the genetic basis of different neurodegenerative diseases, including both pediatric diseases (e.g. Leigh Syndrome), as well as late-onset diseases such as Parkinson's disease and Alzheimer's disease. These studies typically focus on the impact of single genes, and in some cases, have helped us to understand the underlying mechanisms of human neurodegenerative diseases. However, neurodegenerative diseases are complex diseases. Age at onset, severity, and symptomatology are all influenced by large networks of interacting genetic and environmental factors. These factors influence, in turn, downstream 'omic' domains, including the epigenome, transcriptome, proteome, metabolome, and microbiome. To fully understand the complex causes and consequences of neurodegenerative diseases in genetically variable populations living in complex environments (i.e. humans), we need to begin with a genetically variable model system. Then, to discover the mechanisms that link cause to consequence, we need to incorporate a systems biology (omic) approach.

With this goal in mind, Promislow's lab is using systems biology approaches in the fruit fly to identify naturally occurring allelic variants that modify the effects of A β and tau expression in the fly eye. They anticipate completing a full screen of the *Drosophila* Genome Reference Panel (DGRP)—a mapping population of 200 fully sequenced inbred lines—in the coming months. In fact, they have already identified several very promising candidate loci. The next step will be to carry out metabolomic profiling to compare strains that are able to ameliorate the effects of A β /tau expression with those that cannot. As proof of principle, the team has already demonstrated that whole-body metabolome profiles are able to fully distinguish strains that are sensitive vs. resistant to the toxic effects of H₂O₂.

A lively discussion followed the presentation of this work at the ADRC meeting on March 6, 2017. Of particular note, the audience suggested using the DGRP not only to identify novel loci associated with resistance to A β and tau, but also to test genes that are known to affect AD risk in humans, and which have homologs in *Drosophila*—an intriguing suggestion and one that can be pursued immediately, Promislow noted.