Ackert Hall, Room 120
Wednesday, September 18
4:00 P.M.

Coffee and Cookies
Chalmers Hall, Room 168
3:45 P.M.

Biochemistry & Molecular Biophysics Seminar

Modelling neurodevelopmental disorders-associated *Argonaute* mutations in *C. elegans* ALG-1 reveals variant-specific changes in miRNA populations, functional impairment, and target gene disruption

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Regulation of gene expression is critical for animal development. microRNAs (miRNAs), together with their key co-factors, Argonautes (AGOs), post-transcriptionally regulate gene expression by repressing target genes. Recently, de novo variants in human Argonaute AGO1 and AGO2 genes have been reported to cause neurodevelopmental disorders (NDDs). To model how NDD-associated AGO variants may affect miRNA biogenesis and activity, we reproduced AGO variants in a *C. elegans* Argonaute ALG-1. This array of mutations produced distinct effects on *C. elegans* miRNA function, miRNA populations, and gene expression. The unique amino acid substitutions caused developmental and molecular phenotypes ranging from mild loss-of-function to antimorphic phenotypes that indicate that aspects of miRNA processing and miRISC formation/activity are profoundly altered. We believe AGO mutation modeling in a *C. elegans* Argonaute will shed light on the mechanisms of human neurodevelopmental disorders and will advance our understanding of Argonaute functions, providing insights into conservation of miRNA-mediated gene-regulatory mechanisms.