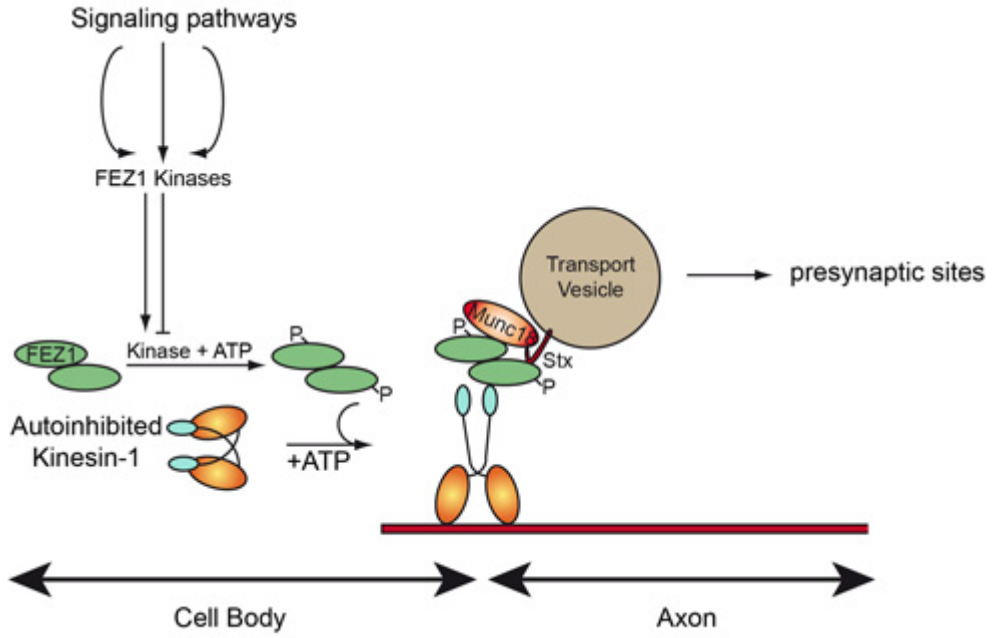
Research

Interactomics and Intracellular trafficking

Protein Trafficking to Synapses

Neurotransmission occurs at specialized contact sites between neurons called synapses. Each synapse comprises over a thousand proteins that are delivered from their sites of synthesis via the intracellular trafficking machinery. The logistics of sorting and transporting proteins to meet the needs of the approximately 10,000 synapses distributed throughout numerous highly elongated neuronal processes represents a particularly challenging task. Disruption of intracellular trafficking and loss of synapses are frequently observed in neurodegenerative disorders and during the aging process. We uncovered an axonal transport pathway in which the Kinesin-1 adapter FEZ1 mediates delivery of Syntaxin-1 to synapses where it is required for synaptic vesicle exocytosis. Phosphorylation of FEZ1 regulates its function in this process. Strikingly, loss of FEZ1 function produces phenotypes reminiscent of defective transport observed in Alzheimer's disease patients and mouse models. Using this system as a model of presynaptic trafficking, our research aims to identify components and regulatory pathways involved in protein trafficking during synapse formation and maintenance. In doing so, we seek to clarify how their defects contribute to synaptic malfunction and ultimately neurodegenerative disorders.

A working model for FEZ1's role in protein trafficking to synapses



Synaptic Interactomics

Ensembles of different proteins participate in various key nano-machineries functioning at the synapse. The lab is interested in identifying and studying how interactions between these proteins contribute to synaptic function and organization. We employed the yeast 2-hybrid system to probe for novel presynaptic interactions for a selection of presynaptic proteins. The interaction between FEZ1 and Syntaxin-1 described above is a direct outcome resulting from this effort. Studies are on-going to elucidate the functional significance of other newly identified interactions.