Accumulation of damaged proteins is associated with age-related neurodegeneration in Alzheimer's and Parkinson's patients. The maintenance of protein homeostasis, or proteostasis, involves the degradation of misfolded and damaged proteins, and is essential for cellular function, organismal growth, and ultimately viability. Sustaining proteostasis is not only a long-term challenge for individual cells but also for entire organisms, since damaged proteins accumulate with stress and aging. Not all tissues are equally susceptible to the toxicity of protein aggregates, suggesting tissue-specific differences in proteostasis pathways.

The ubiquitin/proteasome system (UPS) is a major proteolytic route functioning in a cellular network that maintains the proteome during stress and aging. Degradation of proteins is mainly mediated by the 26S proteasome upon covalent attachment of ubiquitin to target proteins by E1 (activating), E2 (conjugating) and E3 (ligating) enzymes in a process known as ubiquitylation. Our long-term objective is to understand the mechanistic and developmental aspects of protein degradation pathways defined by alternative combinations of E3 enzymes using *Caenorhabditis elegans* as a model organism.

Caenorhabditis elegans is an excellent model for the study of proteostasis systems as it represents among the best-characterized metazoan model organisms with numerous advantages including a completed genome sequence, multiple genetic tools to assess function, and a defined cell lineage with a simple body plan, differentiated tissues, and diverse behavioral and physiological phenotypes available to study various biological and pathophysiological processes. Studies using C. elegans as a model system have greatly contributed to our current knowledge of the proteostasis network, its buffering capacity, and its regulation.

Recent studies have shown that cooperative action of two different E3 ligases CHN-1 and UFD-2 in *C. elegans* enables effective ubiquitylation of the essential, myosin-specific chaperone UNC-45. In addition, CHN-1 forms a protein complex with the parkin orthologue, PDR-1. Combination of E3 ligase complexes that involve CHN-1 supports the formation of alternative ubiquitylation structures that aid in directing substrate specificity. The main objective of proposed research is to establish a picture of proteolytic networks defines by CHN-1-based E3 ligase complexes.